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(54) Title: METHOD FOR SAFELY AND EFFECTIVELY ADMINISTERING A DRUG BY INHALATION

(57) Abstract

A method of treating a patient having a disease with a drug, that is typically toxic or has a narrow therapeutic window, by inhalation by the steps of (a) performing a first filter test on the patient with a tracer material and an inhalation device, wherein the patient is not exposed to the tracer material, to obtain a first set of data; (b) performing a second filter test on the patient with a tracer material and an inhalation device, wherein the patient inhales the tracer material, to obtain a second set of data; (c) optionally performing a deposition pattern test on the patient to obtain a third set of data; (d) determining from the first, and second set of data, and optionally from the third set of data, the patient dosing parameters required to administer a predetermined dose of drug to said patient by inhalation; and (e) administering the drug to the patient with the inhalation device using the determined dosing parameters, where the dosing parameters determine the quantity of drug that the patient will inhale and retain on a total body basis or in the patient's pulmonary system.

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METHOD FOR SAFELY AND EFFECTIVELY ADMINISTERING A DRUG BY INHALATION

This Application is a continuation-in-part of copending U.S. patent application No.09/263,748, filed March 5, 1999.

FIELD OF THE INVENTION

The invention concerns the administration of drugs to the pulmonary system (particularly the lung) in the proper dosage, at the appropriate site so that a patient is treated in a safe and effective manner.

BACKGROUND OF THE INVENTION

The administration of drugs directly to the pulmonary system via inhalation has been an established technique for decades, but has been limited to a narrow range of therapeutic categories and indications. Two major uses of the inhalation route for drug delivery are to provide means for systemic drug delivery and to permit targeted local therapy for respiratory illnesses. Regardless of the rationale for selecting the respiratory route for drug administration, available technology has, until recently, restricted the use to agents with a relatively wide therapeutic ratio so that precise control over drug delivery and deposition characteristics has not been a major issue. However, evolving technology both in drug formulation and inhalation delivery devices has led to a marked expansion in the types of drugs and biotherapeutic agents being developed for administration via inhalation.

The delivery of general anesthetics by inhalation is probably the earliest example of utilizing the pulmonary route of administration to achieve therapeutic levels of an agent at a site distant from the lungs. Other examples of drugs that have received regulatory approval for administration via this route for systemic delivery include ergotamine for migraine and adrenaline as an adjunct for the treatment of anaphylaxis. There is a growing list of diverse compounds that are undergoing preclinical testing or clinical trials for pulmonary delivery as an alternative to repeated and frequent subcutaneous injections or repeated IV administration. These include analgesics such as morphine, biotherapeutics such as insulin, calcitonin, leuprolide,

interferon, colony stimulating factors, growth hormone, and numerous other protein and peptide molecules. There are several theoretical advantages to this delivery route including the extensive pulmonary surface area available for drug absorption, the avoidance of a first pass metabolic degradation by the intestine and/or the liver and the non-invasive nature and "patient-friendly" method of drug delivery.

The delivery of bronchodilators via inhalation is by far the most widely used application of aerosol technology. As these agents have a wide therapeutic ratio, many of the potential concerns with this route of delivery have not been addressed. As different classes of drugs are now being evaluated for aerosol administration, issues such as precise and reproducible dosing and environmental exposure risks must be addressed. The concept of delivering drugs for the treatment of respiratory diseases directly to the target organ is certainly attractive. Much higher local drug exposure can be achieved with doses considerably lower than those that would be required for systemic administration, resulting in lower exposure of non-respiratory tract tissues to potentially toxic drug levels. For example, the administration of pentamidine via aerosol has received regulatory approval for the prevention of Pneumocystis carinii infection in high risk patients. Aerosol delivery is also approved for tobramycin and is being investigated for ticarcillin antifungal agents such as amphotericin, and antiviral agents including ribavirin. The administration of cyclosporine by inhalation is being studied for the treatment of allograft rejection in patients who have undergone lung transplant. Various therapeutic agents for use in patients with cystic fibrosis have been evaluated, and some, for example Pulmozyme, are commercially available. However, the concept of treating pulmonary malignancies, either primary or metastatic, by delivering chemotherapeutic agents or biologic response modifiers directly to the lungs has received little attention

The earliest efforts to treat cancers by inhalation go back at least two decades. However, the intervening time has not resulted in an effective treatment that is in general use. One of the major problems encountered with inhalation chemotherapy, is the delivery of drug to a patient in the desired dosage and the desired pulmonary distribution. Unlike drug administration by the oral or parenteral routes in which one can reliably administer a specified amount of drug regardless of the patient's condition, it is much more difficult to deliver a precise amount of drug by inhalation to a patient having normal pulmonary function much less one who has respiratory tract disease, especially cancer, in which there may be large areas of the lung which

may blocked by tumors. In addition each patient's pulmonary system is unique. A similar problem occurs even for individuals having normal lung function that are being treated by inhalation to prevent metastasis to the lung for example, because of variations in normal lung function. For some drugs like bronchodilators, which are not considered to be highly toxic, the consequences of delivering too much drug to the lung are not too severe. If not enough drug is delivered, the patient requiring bronchodilators will not get relief and an additional dose can be administered. However, with anticancer drugs the consequences can be devastating as shown in Table 1 below.

TABLE 1

		LD_{50} in Animals		Effective Dose in Animals	
	Use in Humans	Dose (mg/kg)	Schedule	mg/kg	Schedule
Cancer Drugs					
Doxorubicin[1,2]	Solid Tumors	14.4[a]	Single	8.0[b]	Q4D x 3
5-FU[1,3]	Solid Tumors	51.9[a]	Q4D x 3	20.0[c]	QD 1-9
Paclitaxel[4,5]	Solid Tumors	82.0[d]	QD 1-5	48.0[e]	QD 5-9
Respiratory Disease Drugs					
Albuterol[6,7]	Airway Disease	> 2000[f]	Single	.003-3.0[g]	--
Triamcinolone[8,9]	Anti-inflammatory	< 5000[h]	Single	0.12[I]	--

References: [1] Houchens DP, Johnson RK, Gaston, MR, Goldin, A, and Marks T. Toxicity of Cancer Chemotherapeutic Agents in Athymic (nude) Mice. Cancer Treat. Rpt. 61:103-104 (1977). [2] Imondi AR. Preclinical Models of Cardiac Protection and Testing for Effects of Dexrazoxane on Doxorubicin Antitumor Effects. Semin. Oncol. 25:22-30 (1998). [3] Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute. In Vivo Cancer Models. NIH Publication 84-2635 (1984). [4] Rowinsky EK, Cazenave LA, Donehower RC. Taxol: A Novel Investigational Antimicrotubule Agent. J. Natl. Cancer Inst. 82:1247-1259 (1990). [5] Rose WC. Taxol: A Review of its Preclinical In Vivo Antitumor Activity. Anti-Cancer Drugs 3:311-321 (1992). [6] Albuterol in AHFS Drug Information (McEvoy, GK ed.) Am. Soc. Of Health-System Pharmacists. Pp. 861-865 (1996). [7] Bosler DC, DeGennaro FC, O'Reilly S, Hey JA, and Chapman RW. Pharmacological Studies of Allergic Cough in the Guinea Pig. Eur. H. Pharmacol. 277:159-164 (1995). [8] Takeuchi M, Kaga M, Tsuga T, Ichinohe M, Okazaki S, Shinpo K, Sudo J and Tanabe T. Study on Toxicity of Halopredone Acetate. (I) Acute Toxicity Study in Mice and Rats. J. Toxicol Sci. 1:1-10 (1985). [9] Luzzani F, Barone D, Galliani G, and Glasser A. Ex Vivo Binding to Glutocorticoid Receptors in the Thymus of the Adrenalectomized Rat. Eur. J. Pharmacol. 87:61-66 (1983).

Footnotes: [a] Swiss mice, intraperitoneal route. [b] P388 and L1210 leukemia, B16 melanoma, Lewis lung carcinoma. [c]K1210 leukemia. [d] Mice. [e] M109 lung carcinoma. [f] Rats, oral route. [g] Guinea pigs. [h] Mice and rats. [i] Rats.

Table 1 illustrates very clearly the dilemma faced when treating patients with antineoplastic drugs. The dose has to be controlled very carefully. This table shows

that the LD_{50} levels and effective dose treatment levels for solid tumors for animals are not far apart. Thus for doxorubicin an effective dose of 8 mg/kg(body weight) is not far away from the LD_{50} dose of 14.4 mg/kg. Doubling the effective dose effectively puts the dose near the LD_{50} level where about half the animals would be expected to die. Paclitaxel exhibits similar properties as doxorubicin. The drug 5-FU is somewhat less toxic than doxorubicin or paclitaxel but exhibits similar properties. For non-antineoplastic drugs such as those used to treat airway disease or for anti-inflammatory drugs the differences between LD_{50} and effective dose are in excess of 1000. For these latter drugs (e.g. albuterol, triamcinolone) a doubling or tripling of the effective dose is inconsequential relative to toxic dose or lethal dose.

The above clearly demonstrates the need for methods and apparatus for delivering accurately controlled amounts of inhaled toxic drugs, particularly inhaled antineoplastic drugs, to patients.

BRIEF DESCRIPTION OF THE INVENTION

Generally the method contemplates the development of a patient specific plan for administering a drug by inhalation. The plan is typically based on the patients disease, disease state, age, the aerosol generator used, the drug to be administered, particle or aerosol size and other drug, carrier, excipient or formulation characteristics, the number of dosing and preparatory breaths, type of breath (e.g. deep or shallow), the pulmonary system distribution and the inhaled amount of a tracer material; apparatus parameters; patient breathing or pulmonary characteristics and the like. The tracer material typically has deposition characteristics substantially the same as the drug to be administered or its administration is corrected for the difference. Inhalation device settings, number of dosing breaths, type of breaths, and so on are typically calculated from information obtained in tests developed in the patient specific plan. The patient specific plan provides a safe and effective method for delivering a predetermined dose of drug to the total body, to the pulmonary system, or to a specific site in the patient's pulmonary system.

Broadly, the invention concerns a method of treating a patient having a disease with a drug by inhalation in a safe and effective manner where the method includes the steps of (a) performing a first filter test on the patient with a tracer material and an inhalation device, wherein the patient is not exposed to the tracer material; to obtain a first set of data; (b) performing a second filter test on the patient with a tracer material

and an inhalation device, wherein the patient inhales the tracer material; to obtain a second set of data; (c) optionally performing a deposition pattern test on the patient to obtain a third set of data; (d) determining from the first, and second set of data, and optionally from the third set of data; the patient dosing parameters required to safely and effectively administer a predetermined dose of drug to said patient by inhalation; and (e) administering the drug to the patient with the inhalation device using the determined dosing parameters. The dosing parameters determine the quantity of drug that the patient will inhale and retain.

More narrowly, in another embodiment of the invention, the method contemplates safely and effectively treating a patient exhibiting a neoplastic disease with an antineoplastic drug by inhalation by the steps of

(a) selecting a breathing pattern, selecting a deposited dose, and selecting a particle size appropriate for treatment of the neoplastic disease;

(b) having the patient complete a set of selected breathing patterns during a set of filter tests while inhaling an aerosol including a carrier and a tracer material, wherein the aerosolized tracer material substantially mimics the deposition characteristics of the drug to be administered;

(c) determining the amount of tracer administered to the total body and optionally the amount and distribution of the tracer in the patients pulmonary system;

(d) determining the number of dosing breaths (NDB) in said breath patterns required to deposit the selected amount of the drug in the patient's body or pulmonary system or portion of the pulmonary system, according to the equation;

NDP= Selected Drug Dose (mg) ÷Drug output from aerosol generator per dosing breath (mg/breath) ÷ Deposition efficiency (%/100)

administering the selected amount of drug for the number of determined dosing breaths. The deposition efficiency used in the calculation is that obtained for the particular site of deposition (e.g. total body, pulmonary system or portion of the pulmonary system. The treatment may be for a neoplastic disease of the pulmonary system such as in the lungs or for treatment or prevention of metastasis from or to the lungs from a neoplastic disease elsewhere.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1 is a schematic drawing of a typical inhalation device and system for administration of drug according to the invention.

Fig 2 is a schematic drawing of the details of the invention for the patient interface and filters used with the filter tests.

DETAILED DESCRIPTION OF THE INVENTION AND BEST MODE

Generally the method contemplates the development of data from a test or tests conducted on the patient prior to administering the drug by inhalation. The data include but are not limited to particle or aerosol size and other characteristics, the minimum number of dosing breaths for good distribution, type of breath (e.g. deep, intermediate, or shallow), the pulmonary system distribution and the inhaled amount of a tracer material; apparatus parameters; patient breathing or pulmonary characteristics; and the like. The tracer material typically has deposition characteristics substantially the same as the drug to be administered or the administration of drug is corrected for this difference. In practice having the tracer material have the same aerosol characteristics as the drug is preferred and practical in a real clinical device. Device settings, number of dosing breaths, type of breaths, and so on are typically selected based on prior tests or determined and adjusted based on data from the tests.

Broadly, the invention concerns a method of treating a patient having a disease with a drug by inhalation in a safe and effective manner where the method includes the steps of (a) administering a tracer material to the patient by inhalation with an inhalation device; (b) determining the amount deposited and optionally the deposition pattern of the tracer material in the patient; (c) determining from the amount of deposited tracer material, and optionally from the deposition pattern of the tracer material; the dosing parameters required to administer a predetermined dose of drug; and (d) administering the drug to the patient with the inhalation device using the determined dosing parameters.

The inhalation device typically used with the present invention may be any inhalation device that is capable of delivering the desired amount of drug or antineoplastic drug dose having the required aerosol properties for proper deposition such as particle size, weight, charge, and so on. Typical devices include those generally used in the application of aerosols to patients for treatment of disease conditions. One preferred device is a pulmonary dosing system disclosed in US

regular patent application entitled "Pulmonary Dosing System and Method" filed contemporaneously herewith on March 5, 1999, Serial No. 09/263,986, having the same assignee as the present application, the disclosure of which is incorporated by reference as if fully rewritten herein. The inhalation device disclosed in the aforementioned application will be referred to hereinafter as the Battelle inhalation device.

Definitions

Drug - as used throughout the specification the term "drug" should be interpreted to include any appropriate respirable, therapeutically active material useful in the treatment of disease. While the method can be used with any drug, the method finds particular usefulness with drugs that are toxic or highly toxic and/or that present narrow therapeutic windows.

Antineoplastic drug - as used throughout the specification the term "antineoplastic drug" should be interpreted to include any appropriate respirable, therapeutically active antineoplastic material.

Antineoplastic material - as used throughout the specification the words should be interpreted to include materials useful in the treatment of cell growth where the growth is uncontrolled and progressive. Typical terms that are included in this category to describe uncontrolled cell growth are cancer, tumor, neoplasm, neoplasia and the like.

Dosing Breath - The inhalation breath which carries the tracer material aerosol or drug aerosol to the appropriate site in the pulmonary system (e.g. a deep inspiration dosing breath will favor deposition deep in the respiratory tract).

Total Deposited Dose (TDD) - The amount of drug to be deposited in the body expressed as mg/m^2 body surface area.

Deposition Efficiency (DE) - The fraction of the nebulized drug deposited in the body or "retained/nebulized" in the Tc-99m deposition test.

Pulse volume - The volume of drug solution (mL) aerosolized per activation of the aerosol generator. The useful pulse volume for different types of aerosol generators is typically in the range of about 0.001mL to about 0.1 mL. The pulse volume should be substantially the same in aerosol generators that are used for the filter tests and in drug administration. In the examples herein the aerosol generator was a nebulizer having a mean pulse volume of about 0.023 mL that ranged from a

high of 0.0272 mL to a low of 0.0199 mL. A narrow range is best as explained below.

Drug/pulse (D/P) - The amount of drug (in mg) aerosolized per activation (pulse) of the nebulizer. D/P = concentration of the drug solution (mg/mL) x pulse volume (mL). This pulse is pulse available for inhalation. In the examples below the drug is doxorubicin but may be any antineoplastic drug capable of being inhaled.

Total Doxorubicin Dose - The total amount of doxorubicin which should be administered (total deposited dose x body surface area (BSA)).

Dosing parameters - this term refers to the parameters used to control exposure of the patient to a drug or a tracer material. In one embodiment of the invention the dosing parameters that are determined are the number of breaths that the patient should take to receive the predetermined dose of drug. Besides the aforementioned number of dosing breaths, other dosing parameters that can be determined by the method of the invention include (1) time, such as the measurement of exposure time during the breathing cycle as one of the set of data measured in the filter tests during which the patient is exposed to a tracer material and determining the corresponding time that the patient should be exposed to a drug during the breathing cycle in which drug is administered to the patient; (2) weight or volume reduction in the supply of tracer material or drug at the aerosol generator, the measurement of weight or volume reduction at the aerosol generator during the filter tests would then be used to determine the weight or volume reduction in the supply of drug; (3) the converse of (2) would be track the amount of tracer material used and to monitor the patients use of drug in the supply of drug at the aerosol generator; (4) and in a final embodiment the amount of aerosol that is generated by the aerosol generator during the filter tests and drug administration session.

Number of Dosing Breaths (NDB) - The number of dosing breaths required to deposit the predetermined dose of drug to the appropriate site in the patient's pulmonary system. The formula to determine the number of dosing breaths is listed below:

$$\text{NDB} = \frac{\text{Total Doxorubicin Dose (mg)}}{\text{DE}} \div \text{Drug Amount/Pulse (mg)}$$

Tracer material - a material that is detectable, the tracer material may contain radioactive isotopes with short half-lives that upon disintegration produce emissions that are detectable by imaging or other radioactive measurement techniques (e.g. Tc-99m DTPA and the like). Although only Tc-99m DTPA has been used in the present examples it is contemplated that Tc-99m attached to other molecules is useful in the invention as are other types of isotopes. The tracer material is typically in the form of a powdered particulate or an aerosol. The tracer is typically used alone or physically mixed with or chemically attached to another material with which it forms a predetermined particle or aerosol size or range of sizes. In other embodiments the tracer material may be fluorescent, absorbent, colored, dense, or in any form where a detectable signal may be obtained. When Tc-99m and the like is used the total amount of Tc-99m may range from 0.1 mCi to 10 mCi but preferably about 1 mCi to 3 mCi. The actual amount of Tc-99m placed into the nebulizer may be determined by any suitable means for detecting gamma radiation, e.g. gamma camera or gamma well counter.

Substantially impaired pulmonary system means that there are areas of the lung that have substantially complete blockage of at least some portions of the pulmonary system such that the drug would concentrate in certain regions at concentrations likely to produce toxicity. Also cases where the patient is unable to have the drug delivered to areas of the pulmonary system (e.g. portions of the deep lung) so that the drug concentrations in the proximal airway or larynx would cause laryngitis, etc.

Substantially normal pulmonary system means that based on examination of the patient, including any pulmonary test, the patient is functioning substantially as a normal patient. Further, the pulmonary system appears to be in a condition where the drug can be distributed uniformly or distributed to the target region of the pulmonary system.

Low risk category with regard to the administration of the drug means that from examination of the patient including any pulmonary test the patient is functioning substantially as a healthy normal person. There is a relative high probability that the patient would not experience toxicity from the inhaled drug dose.

High risk category with regard to the administration of the drug means that the patient is likely to experience toxicity or other adverse reactions if the drug is inhaled.

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One of the major problems with inhalational chemotherapy is the delivery of accurate amounts of drug to a patient. It is believed that this factor is largely responsible for the fact that inhalational chemotherapy, pioneered by Shevchenko in Russia in 1968, and Sugawa and Tatsumura in Japan in 1970 and 1983 respectively, has not been universally accepted for cancer treatment in the pulmonary tract. Unlike drug administration by oral or parenteral routes in which one can reliably administer a specified amount of drug regardless of the patient's condition, it is much more difficult to deliver a precise amount of drug to a patient by inhalation. This is particularly true for a patient who has a respiratory tract disease, especially cancer, in which there may be large areas of the lung which are blocked by tumors or airflow is otherwise restricted. For some drugs like bronchodilators, which are not considered to be highly toxic, the consequences of delivering too much drug to the lung are not too severe. However, with anticancer drugs, the consequences of overdosing can be devastating.

The use of tracer material in scintigraphy (e.g. in Tc-99m scintigraphy and the like) is a well-known medical diagnostic and research procedure in pulmonary medicine. This procedure has been used to show how an inhaled aerosol distributes in the respiratory tract and has aided in the evaluation of new improved inhalation drug devices. It has now been found that the use of tracer materials such as Tc-99m in scintigraphy provides a safe and useful tool in controlling and delivering the correct amount and pulmonary distribution of highly toxic drugs such as antineoplastic drugs to be given to patients by inhalation.

In one embodiment of the invention, patients who are candidates for inhalational chemotherapy using highly toxic drugs or drugs with narrow therapeutic windows will undergo a first and second filter test with a quantity of tracer material that mimics the deposition pattern of the drug to be administered. In a preferred embodiment, the tracer material will contain particles having Tc-99m as a tracer. The first filter test will have an inhalation filter that filters out all tracer material that the patient would have inhaled. A second filter test is performed but the inhalation filter is removed and the patient actually inhales the tracer material. Data from the first and second filter tests will be used to determine the amount of tracer material that is retained in the body of the patient. Following inhalation in the second filter test, if desired, the distribution of the inhaled Tc-99m in the pulmonary system can be determined by the usual methods (such as with a gamma camera). The information

can then be used to determine the inhalation conditions for administering the drug to the patient. For example inhalation conditions typically include one or more of the following, but is not limited by the list, the various settings of an inhalational device, breathing pattern of a patient, aerosol particles sizes, number of dosing breaths to be taken by the patient, the time length of a dosing period for administering a desired dose to the patient, volume or weight of drug and carrier to be aerosolized, and so on.

Aerosol Generation

Aerosols are generated by suspending particles of a solid or a liquid in a gaseous medium. There are three major categories of devices for the generation of aerosols for inhalation that are in clinical use. These include metered dose inhalers, dry powder inhalers and nebulizers. The device used depends on the medical indication, the formulation, and the characteristics of the agent administered. Any of these devices are useful in the present invention as long as aerosols having desired properties are obtained.

Metered dose inhalers utilize a liquid propellant provided in a container and equipped with a metering valve that dispenses a constant volume of a solution or suspension of the drug in the propellant. Some patients experience difficulties in coordinating inhalation and exhalation with activation of the device and inhalation technique is critical for optimal drug delivery. A further drawback to this type of device is that substantial oropharyngeal deposition occurs because of the characteristics of the droplets generated and the velocity of the aerosol expelled from the device. Some of the difficulties with inhalation techniques and particle size have been overcome by the use of spacer devices.

Dry powder inhalers do not use a propellant. They are breath-activated and therefore, patient coordination is not as important an issue. Many of these devices are designed to utilize the patient's inspiratory effort for aerosol dispersion and delivery of the drug powder to the lung. The drug is formulated in a filler and contained in a capsule, which is placed in the device and punctured to release the powder. Both single load and multidose systems are available.

Aerosol formation by nebulizers is typically achieved by a high-velocity airstream forcing a solution or suspension of the drug through a liquid critical orifice (jet nebulizers), ultrasonically by the vibration of a piezoelectric crystal (ultrasonic nebulizers), by other methods such as electrical forces, or by combinations of the above. As is the case with dry powder inhalers, nebulizers are typically activated by

patient respiration and drug deposition is dependent upon flow rate. Therefore, patient cooperation and coordination is not as critical as with metered dose inhalers.

Electrohydrodynamic aerosol generation devices are particularly useful for the practice of the present invention because they can generate aerosols having the needed properties and a very small variation the particle sizes. Electrohydrodynamic aerosol generation is a process where bulk solutions are aerosolized using electrical forces. In a typical electrohydrodynamic spray nozzle, the fluid to be aerosolized flows over a region of high electric field strength. When it does so, it receives a net electric charge that tends to stay on the surface of the fluid. Hence, as the fluid exits the nozzle, the repelling force of the surface charge balances against the surface tension of the material, and a cone is formed (known as a Taylor cone). The tip of the cone has the greatest concentration of charge, and at this point, the electrical force overcomes the surface tension, generating a thin jet of fluid. The jet breaks up into droplets of more or less uniform size, which collectively form a cloud. In some applications, it is advantageous to maintain the imparted charge on the droplets. The charge provides a mechanism for improved adhesion. In medical applications like pulmonary drug delivery, the droplets are typically discharged, by exposing the cloud to a stream of ions having an opposite polarity. The result is an aerosolized solution having a monodispersed droplet size and near zero velocity. Such a cloud is particularly desired in medical pulmonary applications such as with the present invention.

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Following is a detailed description of the invention and the use of the method of the invention for determining and administering a safe and effective dose of drug to the patient. The method may use any aerosol generator that can reliably generate an aerosol having the required properties. The method for safely and effectively treating a patient exhibiting a disease with a drug by inhalation first contemplates developing data useful for determining the proper inhalation conditions for administration of the drug to the patient. The data is developed by testing a patient with an inhalation device that is the same device or substantially the same device as that which will actually be used to administer the drug.

A typical device useful for testing the patient and administering the drug is shown in Figure 1. The typical inhalation device 100 includes an aerosol generator 110 that provides a supply of aerosol via connection to 111 to patient interface 120. An air or gas supply 130 is typically connected to the aerosol generator 110, via

connection 131, and/or to the line 111 via connection line 111, and/or to the patient interface 120. Depending on the type of aerosol generator all three or only one or two of connection lines 131, 132, or 133 may be needed. Typically device 100 includes an exhaust filter 140 connected to patient interface 120 via connection line 141 for filtering exhaled and blow-by gases to remove drug or tracer materials. Besides its use as an environmental filter, the amount of tracer material retained in the exhaust filter 140 (when replacement filter 164 is not used, see Figure 2) is useful in the calculation and determination of the dose of drug deposited in the patient as explained elsewhere herein. A check valve 144 or similar device for maintaining one directional flow may be used as needed in the device such as connected to the outlet of exhaust filter 140 via connection line 143 or in other locations. If the valve is located at the outlet of exhaust filter 140 it will not be contaminated unless there is a leak in the exhaust filter 140. Control unit 150 for controlling various aspects of the inhalation device 100 may include signal processing means, memory, software for control of various functions of the device, sensors, operator interface means such as printers, video screens, lights, sound devices and the like that provide visual, acoustic, or printed indications to an operator. A typical control unit 150 may include a PC or similar computer unit and associated software. The software may be typical of that used in the art for controlling gas flow, liquid flow, on-off cycles, temperature; for calculating breath cycles, duration of breaths, and the like. Typically electrical or other sensing and control lines 153 are used to interconnect the various portions of the device 100 as shown in Figure 1. In a preferred embodiment look up tables representing calculations for body surface area, lung surface area or volume, scintigraphic readings, risk factors, and other measurements needed for calculations are included. A further typical embodiment includes a neural network in control unit 150.

An optional plenum 109 may be used at the outlet of aerosol generator 110 in some versions of the inhalation device as in the Battelle inhalation device. Plenum 109 functions to receive aerosol from the aerosol generator 110 and to allow the aerosol to slow down and stabilize prior to inhalation by the patient via connection line 111 and patient interface 120. Plenum 109 may optionally have its own supply of air from air supply 130 via line 134. When plenum 109 is not present aerosol generator 110 is connected directly to the patient interface 120 via line 111.

Air supply flows and pressures to the various parts of the inhalation device 100 may be preset or controlled by control unit 150. Air pressure and flow requirements will vary depending on the application, aerosol generator and so on. In the Battelle inhalation device, for example, the aerosol generator 110 is a nebulizer that requires high-pressure airflow to produce the aerosol.

Container 190 encloses a tracer material formulation 191 that is used with the inhalation device 100. Tracer material formulation 191 is selected to substantially duplicate the aerosol properties of a drug to be administered to the patient. Container 195 encloses a drug formulation 196 to be administered to the patient, this drug formulation has properties when aerosolized that are substantially duplicated by tracer material formulation 191.

Referring now to Figure 2, a schematic drawing of the patient interface 120 is shown illustrating details of one embodiment of interface 120. The patient interface 120 may be any device that allows effective testing and treatment of the patient. One embodiment of the patient interface uses Y-connector 121 that connects the patient to the inhalation device 100. Inlet leg 122 of Y-connector 121 is connected to connection line 111 that provides a flow of aerosol and gas or air. Outlet leg 123 of Y connector is connected to connection line 141. A mouthpiece 125 is connected to Y-connector 121 at common arm 124. Nose clip 121 is typically used to prevent nasal inhalation or exhalation. As used herein the term mouthpiece includes all means (e.g. mouthpiece, mask) for securing or operatively connecting the device 120 and administering drug or tests to the patient and will be generally used in the discussion herein. An inhalation filter 161 is typically located at the mouthpiece 125 or at common leg 124. Inhalation filter 161 intercepts and captures substantially all of a tracer material, drug or other aerosolized material that is drawn into contact with the filter 161 as the patient inhales during the first filter test phase of the method. Bypass filter 163 captures substantially all of the aerosolized material flowing from connection line 111 that bypasses filter 161 and enters leg 123 of the Y-connector as the flow of gases flows toward and into connector 141. The patient interface is constructed so that the device 100 is sealed and usable with the filters 161, 163 present or removed. When filter 161 is used it is placed so that all air inspired from device 100 by the patient is filtered and is of a type wherein substantially all aerosol particles are removed so that the patient is not exposed to the aerosolized tracer materials.

In some embodiments it is contemplated that the typical inhalation device that is used to administer the drug is not actually the same device used in the tests but is substantially similar to that used in the tests. A substantially similar device may be used for example when the tracer material 191 is radioactive. In this case, in order to reduce patient and clinical worker exposure to radioactive materials it is contemplated that portions of inhalation device 100 that are contaminated with radioactive tracer material be replaced. Examples of replaceable portions include nebulizer portions, piping or ducts, the patient interface, filters, and so on. In some cases it may be advantageous to replace the entire inhalation device 100. A substantially similar device is considered to be one that acts substantially the same way as the original tested device. Acting substantially the same way includes for example generating an aerosol having substantially the same particle size distribution and properties that provides substantially the same deposition and distribution characteristics in the patient, generating substantially the same amount of aerosol in given time period, and so on. An example of a substantially similar device would be a device from the same manufacturer of the same model type or design. Preferably the substantially similar inhalation device has properties that provide patient drug deposition amounts or distributions that are within 20% of the amounts and distributions of materials in the tested device, more preferably within 10% of the tested device and most preferably within 5% of the tested device (e.g. the generation of aerosol such as the pulse volume in the Battelle inhalation device should be narrowly controlled to assure the substantially the same deposition amounts during the drug dosing phase as during the testing phase). The closer the properties are to the tested device the greater the ability to provide safe and effective treatment.

Presently Preferred Device

A presently preferred device with which to practice the invention is the Battelle inhalation device. This device provides the necessary elements for successful patient testing and administration of drug. Two of the key elements for the successful delivery of drugs via inhalation are the generation of aerosols having appropriate properties for delivery to the target in the patient and the ability to deliver an accurate dose in a reproducible fashion. Particle size and flow rate are major parameters that determine the site of deposition within the respiratory tract which may range from maximal deposition in the oropharynx, trachea or main bronchi to deposition deep in

the lungs. Reproducibility of dosing in inhalation devices also depends on the breathing characteristics of the patient and there may thus be considerable inter- and intrapatient variability.

The Battelle inhalation device is typically for mouth only respiration although the device can be used for nasal inhalation when treatment of the nasal passages is required. When triggered by automatic mode or by a therapist, the control unit controls the gas supply pulse to the nebulizer for a predetermined time interval. The atomized drug accumulates in a plenum 109 and is inhaled naturally by a patient through a dosing breath.

Typically the patient breathes fresh air during the normal preparatory breaths of the cycle although various medicines may be incorporated in the air to assist the patient in controlling his/her breathing, reduce coughing, dilate the bronchi and so on. Near the end of the second inhalation aerosolized drug will be generated via a nebulizer (the Battelle inhalation device preferably uses a Pari LC Plus nebulizer) and pressurized air from the air supply. Once generated, the aerosolized drug decelerates and accumulates inside the plenum 109 until it is pulled into the patient's lung naturally upon a dosing breath.. Upon inspiration the patient is typically reminded by the operator or the inhalation device to perform a breath hold which will increase drug deposition. The patient's expired air then passes through a Pall HME 15/22 exhaust filter before being released from the inhalation device.

Typical Devices

Pulmonary administration by inhalation may be accomplished by means of producing liquid or powdered aerosols, for example, by the devices disclosed herein or by using any of various devices known in the art. Various delivery devices are commercially available and all or portions thereof can be employed, e.g. Ultravent nebulizer (Mallinckrodt, Inc, St. Louis, MO); Acorn II nebulizer (Marquest Medical Products, Englewood, CO); Ventolin metered dose inhalers (Glaxo Inc., Research Triangle Park, North Carolina); Spinhaler powder inhaler (Fisons Corp., Bedford, MA) or Turbohaler (Astra). Such devices typically entail the use of formulations suitable for dispensing from such a device, in which a propellant material may be present. Ultrasonic nebulizers may also be used.

Nebulizer devices such as those in Greenspan et al US patents 5,511,726 and 5,115,971 are useful in the invention. These devices use electrohydrodynamic forces

to produce a finely divided aerosol having uniformly sized droplets by electrical atomization. While the Greenspan devices use piezoelectric materials to generate electrical power any power source is acceptable to produce the electrohydrodynamic forces for nebulization.

Elecrohydrodynamic devices such as those disclosed in the following patents or patent applications are useful in the invention: see for example US 4,358,059; US 4,765,539; US 4,801,086; US 4,962,885; WO 94/12285; WO 94/14543; WO 95/26234; WO 95/32807; and WO 95/26235.

Formulations for Tracer Material and Drug

Formulations for the tracer materials and drugs used herein are selected so that the tracer material substantially duplicates the aerosol properties of the drug with which it is used. This duplication or mimicking of properties important in the deposition of drug in the pulmonary system allows the use of a tracer material for deposition tests without the presence of the drug. Because the patient is not exposed to the drug in the test phase risk of injury to the patient is reduced.

A tracer material formulation that has been found useful for tests in the delivery of doxorubicin is a 20/80 (v/v) ethanol/water mixture of Tc-99m DTPA. This formulation produces an aerosol whose aerosol properties (e.g. particle size) and pulmonary deposition properties substantially mimic or duplicate those of a 20/80 ethanol /water (V/V) doxorubicin formulation. Because of.the similarity of the particle size and other characteristics, a Tc-99m DTPA filter test and the optional scintigraphy test practiced according to the method of the invention can serve as a means of predicting total body deposition or pulmonary doxorubicin deposition and distribution and be used to determine dosing parameters (e.g. number of dosing breaths) required to achieve the deposition of a specific quantity of doxorubicin in the total body, pulmonary system, bronchi or lung. The ratio of ethanol to water in the above formulation may be varied to the extent that it does not substantially alter the pulmonary deposition properties of the aerosol containing the tracer material or drug.

Formulations having substantially the same aerosol properties and deposition properties for a particular tracer material and a particular drug can readily be ascertained by those skilled in the art once knowing the teachings of the present invention. Included in these formulations are tracers based on radioactive materials such as Tc-99m, dense materials, colored materials, fluorescent materials and the like.

Additional drugs typically included in the formulations are drugs having high toxicity or narrow therapeutic windows such as antineoplastic drugs, certain highly toxic antibiotics, and antivirals. Specific examples of antineoplastic drugs include taxanes such as paclitaxel and docetaxel; vinca alkaloids such as vincristine, vinorelbine, vindesine, and vinblastine; anthracyclines such as daunorubicin, methoxymorpholino doxorubicin, epirubicin, cyanomorpholinyl doxorubicin, and idarubicin; carboplatin and cisplatin. Additional drugs included in the formulations of the present invention are antineoplastic agents not mentioned above but included in the groups represented by alkylating agents, DNA crosslinking agents, antimetabolites, topoisomerase inhibitors; and tubulin inhibitors.

Included within the formulations of the present invention are aerosols containing liposomes and other particles that enclose drugs, or that have drugs attached to their surface, and are useful in the treatment of disease.

Various physiologically inert gases may be used as an aerosolizing agent for the formulations. Other components such as physiologically acceptable surfactants (e.g. glycerides and particularly lung surfactants), excipients (e.g. lactose), carriers, preservative agents, and diluents may also be included in the formulations. Of particular value are typically chemoprotectants that may be added to the formulations and used to protect the pulmonary system from the toxic effects of the drugs. A typical example of a useful pulmonary protectant is dexrazoxane.

The solution or suspension of the Tc-99m DTPA and/or drug may be any pharmaceutically acceptable vehicle such as water, ethanol, PEG or combinations thereof so long as the herein-required properties for the aerosol are obtained. The solution or suspension may also contain other surfactants such as lecithin or other phospholipids, to facilitate the deposition of the DTPA under conditions where large amounts of mucus may be present. Materials specifically added to alter aerosol properties to obtain the required aerosol properties may also be present. The important factor to keep in mind in making the various formulations is that the tracer material, and its carrier and any associated materials carried therewith, must have the substantially the same deposition characteristics as the drug that will later be administered to the patient.

Aerosol or Particle Size

The aerosol particle size used in the method will be determined by the deposition site selected for treatment. Smaller particles are needed for treatment in the deep lung while larger particles are need for treatment of the proximal respiratory tract such as the bronchi. Typically particle sizes between 0.1 and 10.0 micrometers are useful in the present invention. For deposition within the central and peripheral compartments of the lung the particles should typically have a particle size of from about 1.0-5.0 μm with a GSD less than about 2.0. As is known in the art, particle sizes are selected depending on the site of desired deposition of the drug particles within the respiratory tract.

Drug Dosage Recommendations

Since the procedures described herein and the dose of inhaled drug for highly toxic drugs and those with narrow therapeutic windows is rather new, the following guidelines for these and particularly new and untested drugs may be useful to the practitioner. It is recommended that the initial dose of inhaled drug for human patients be about 1/20 to 1/2 of the maximum tolerated dose from a dog toxicity study in which the drug is administered to the dog by inhalation. A more preferred initial dose for some drugs is 1/10 to 1/3 the maximum tolerated dose for the dog. The maximum tolerated dose in the dog is defined as the lowest dose of drug that produces mild to moderate microscopic pulmonary toxicity but no change in respiratory rate. Typically this inhaled dose in the dog is either the lung or total body deposited dose based upon a Tc-99m deposition test. The Tc-99m is typically incorporated in the drug solution as a tracer. The drug is administered to the dog via an inhalation device that does not have to be the same but may be the same or substantially the same as that used to treat the patient. The initial human patient doses can be escalated as needed during treatment up to dose limiting toxicities in the patient by methods known to practitioners in the art. The ultimate dose in human patients is typically 1/10 to twice that of the maximum tolerated dose in the dog as defined above.

For doxorubicin administration, the recommended initial starting dose for humans is about 0.13 mg/m^2 (based on body surface area) to about 0.4 mg/m^2 or about 1/10 the low dose (1.3 mg/m^2 single dose) to 1/3 the maximum tolerated dose from a dog toxicity study in which aerosolized doxorubicin was administered via an endotracheal tube. The maximum tolerated dose in the dog was administered three

times at biweekly intervals and produced mild to moderate microscopic pulmonary toxicity but no change in respiratory rate as seen in dogs given higher doses. It is believed that 0.13 - 0.4 mg/m^2 (body surface area), given every three weeks for three administrations is an appropriate starting dose for humans. If tolerated, this dose can be escalated using predefined dose escalation criteria. Additionally, doxorubicin inhalation should be administered in a manner matched to the patient and particular neoplasm being treated.

Additional guidelines for dosages include those disclosed in copending US application for "Formulation and Method for Treating Neoplasms by Inhalation" filed concurrently herewith having attorney docket number 22000(1)9711CIP, Michael E. Placke et al, and the same assignee as the present application, the contents of which are incorporated by reference as if fully rewritten herein. The application particularly provides teaching of doses for the safe and efficacious inhalation of doxorubicin, paclitaxel, vincristine, vinorelbine, cisplatin, etoposide, 9-aminocamptothecin, and carboplatin. A portion of the guidelines included therein are repeated below:

The safe and effective range of doses of the inhalant antineoplastic drugs in humans and animals (e.g. dogs and similar small animals) are shown in Table 2 below. Larger animal dosages can be calculated by using multiples of the small animal based dose based on the known relationship of body weight to kg/m^2 of body surface area. The exact doses will vary depending upon such factors as the type and location of the tumor, the age and size of the patient, the physical condition of the patient and concomitant therapies that the patient may require. The dosages shown are for doses for one course of therapy. A course of therapy may be given, monthly, weekly, biweekly, triweekly or daily depending on the drug, patient, type of disease, stage of the disease and so on.

Table 2

Doses for Several Antineoplastic Drugs for a Course of Therapy

Drug	Animal Dose* mg/m^2	Human Dose* mg/m^2
Doxorubicin	0.2 to 90	0.4 to 130
Paclitaxel	1 to 270	1.5 to 400
Vincristine	0.06 to 2	0.1 to 3
Vinorelbine	1.3 to 60	2 to 90
Cisplatin	4.6 to 200	7 to 300
Etoposide	4.6 to 200	7 to 300
9-Aminocamptothecin	0.026 to 10	0.04 to 15
Carboplatin	0.12 to 8	0.24 to 16

* - m^2 body surface area

As is known by those skilled in the art, a course of therapy may include one dose to an extended dosage period lasting many months. A course of therapy may include a minimum dose listed above or may include levels of drug that add up to the amount specified. For example, where the patient is to receive 0.4 mg/m^2 of doxorubicin in a particular treatment session, the drug is typically administered in small amounts over several breaths. Where the drug is administered over 20 breaths in a one day session the patient would receive 0.02 mg/m^2 at each breath. However, the daily course of therapy would be considered to be 0.4 mg/m^2. If the patient receives this one-day dose once a week for a six-week period the course of therapy is considered to be 6 x the daily dose or 2.4 mg/m^2. As noted above, the doses may be given in single or divided amounts on a daily, multiple days, weekly, bi-weekly or monthly and may be repeated as needed to achieve the desired effects on the particular lung or respiratory tract tumor being treated or prevented. As noted the drugs are typically administered in cycles , that is the patient is treated for one or more periods after which there is a rest period of days or weeks. The treatment is then repeated. The inhaled drugs may be given alone or in conjunction with drugs administered by other routes such as IV, oral, intrapleural, or intratumoral for treating or preventing tumors outside of the respiratory tract.

Carriers useful for the drugs listed herein are those that provide ease of delivery to the patient by inhalation and are nontoxic in the concentrations administered. Water, PEG, alcohol, propylene glycol, glycerol, and mixtures thereof are typical carriers presently preferred in the invention. Drug concentration in the carrier may range from zero to saturation depending on the test or treatment involved, preferably 0.001 mg/mL to saturation.

Exemplary safe and effective amounts of carrier are given for each product have been published by the respective manufacturer and are summarized in the Physicians Desk Reference. For carriers and formulations useful with electrohydrodynamic devices reference is made to formulation characteristics including carrier materials disclosed in a provisional application for Therapeutic Formulations for Aerosolization and Inhalation, Serial No. 60/132,215, filed May 3, 1999, having the same assignee as the present application, the contents of which are incorporated by reference as if fully rewritten herein.

Patient Training

Typically the patient is trained in the type of breathing and the number of breaths required for the effective treatment of the patients disease state. For example, if deep lung deposition is desired the patient is trained to take deep dosing breaths and to retain them for a set period of time. This series is continued for the number of dosing breaths the patient requires. For deposition in the proximal airways shallower dosing breaths are practiced along with optional breath holding for the required number of breaths. Typically, the patient performs the training sessions in conjunction with the inhalation device so that the patient is familiar and comfortable with its use. Patient breathing training in conjunction with the inhalation device and the method of administration of the present invention will result in more efficacious treatment.

<u>Testing and Dosing</u>

There are three main embodiments of the invention. A first embodiment contemplates performing a two step testing procedure for a patient that is determined to have a substantially normal pulmonary system followed by administering a drug based on the test. A second embodiment contemplates performing a three step testing procedure on a patient that is determined to have a substantially impaired pulmonary

system followed by administering a drug based on the test. A third embodiment contemplates performing an evaluation of the patient to determine the category "substantially normal or repeat patient" or "substantially impaired or at high risk" into which the particular patient fits followed by the testing procedure for that category. Typically, a substantially normal or repeat patient would be treated with the two step testing procedure and a substantially impaired or high risk patient would be treated with the three step testing procedure.

A. Two Step Filter Test Procedure

The two step filter testing procedure contemplates developing dosing information for the individual patient using the following steps. The first step includes a set of filters (inhalation filter 161 and blow-by filter 163) and is called the first filter test. The second step (the second filter test) dispenses with at least the inhalation filter and applies a tracer material directly to the pulmonary system of a patient. Both the first filter test and the second filter test develop data that is used in determining dosing information for treatment of the patient with the inhalation device 100. The patient is instructed to breathe through the mouthpiece for a set number and type of breaths. Typically the breaths contemplated include a set of preparatory breaths numbering from zero to 20 during which no aerosolized tracer material is released by the inhalation device and a dosing breath for which a controlled dose of tracer material is released. The patient then repeats the breathing procedure a predetermined number of times, typically zero to twenty times, more preferably one to ten times. Most preferred is the actual breathing procedure used in the examples herein, two preparatory breaths followed by a dosing breath, with the breathing procedure repeated a total of five times. A typical breathing sequence that is expected to provide good results for the filter test uses at least one to six preparatory breaths followed by a dosing breath and a breath hold period for each dosing breath. This sequence is repeated from one to six times. Although no aerosol is actually inhaled during the first filter test, a breath hold period may be useful during the first filter test to provide similar conditions as in the second filter test. In addition a breath hold period will aid in patient training and compliance during the second filter test. The breath hold period will follow the dosing breath and will be from zero seconds (corresponding to no breath hold) up to 30 seconds. It is important to note that the

breath hold period in the first filter test is typically selected on the basis of the desired breath hold period in the second filter test.

The preparatory breaths are typically normal breathing breaths; but, may be any found useful for providing good patient compliance and proper dosing during the following dosing breath. The dosing breaths and the following breath-holding period are typically those found to provide proper pulmonary deposition and pulmonary distribution. In the latter regard previous studies such as Bates, DV et al; Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract; Health Physics; Pergamon Press; Vol. 12; 1966; pp. 173-207; Brain, JD et al; Deposition of Aerosol in the Respiratory Tract; Am Rev Resp Dis; 1979; Vol. 120; pp. 1325-1373; and Bennett, WD et al; Human Variation in the Peripheral Air-Space Deposition of Inhaled Particles; J Appl Physiol; 1987; Vol. 62; pp1603-1610 provide guidelines useful for determining deposition sites and other characteristics of inhaled aerosols that may be useful for administering tracer materials and drugs according to the teachings of the present invention. In addition to these studies, deposition parameters found for the individual patient using the tests of the present invention may likewise be used in a subsequent test session to properly test and treat the patient. Because of disease progression or other variables present in an individual patient, one or more additional deposition tests may be needed, even with preliminary guidelines from previous deposition studies, in order to properly dose the patient. However, it is contemplated that, except for very severe cases, usually one test will suffice and two tests will almost always be sufficient.

When the patient performs the aforementioned dosing breath, a tracer material is released as an aerosol and administered to the patient. Of course, because of the presence of inhalation filter 161 during the first filter test no tracer material actually reaches the patient but is filtered out and captured on inhalation filter 161. At the same time blow-by tracer materials are captured on blow-by filter 163. Subsequently, the inhalation filter 161 and blow-by filter 163 are removed and tested for the amount of tracer material present. Tracer material testing is a well-known technique and known techniques such as the use of well counters for radioactive materials; detectors for fluorescent materials, color detectors for color, or absorption; and the like are contemplated for the test herein. Specifically preferred is Tc-99m. Using information including the amount of tracer material nebulized, the amount of tracer material captured on the inhalation filter 161, and the amount of tracer material captured on the

by-pass filter 163, radioactive decay times, and the like, the amount and relative percentage of tracer material that is present on the inhalation filter can be determined. The amount of tracer material present on the inhalation filter 161 represents the amount of tracer material that would have been inhaled but for the presence of the inhalation filter 161.

In a second test, termed the second filter test, the foregoing procedure is essentially repeated except that inhalation filter 161 is removed and exhaust filter 140 or an optional replacement blow-by filter 164 (that replaces blow-by filter 163 that was removed for analysis in the first filter test) is used to measure blow-by and exhaled tracer material. The replacement blow-by filter 164 may be dispensed with if an exhaust filter 140 is used and analyzed, however, a replacement blow-by filter 164 is preferred in order to obtain similar operating conditions. The patient breathes through the mouthpiece as before but for a new set of predetermined number of breaths. Typically the breathing pattern includes a set of preparatory breaths (typically numbering the same as in the first filter test and of the same type) during which no aerosolized tracer material is released by the inhalation device. Following the preparatory breaths, a dosing breath is taken for which a controlled dose of tracer material is released and inhaled followed by a breath hold period. The breath hold period may be any period from zero seconds (corresponding to no breath hold) up to 30 seconds. The breath hold period selected is that which will provide proper deposition of aerosol at the desired site in the pulmonary system. The patient repeats the preparatory breaths, dosing breath, and breath hold breathing procedure a predetermined number of times, typically five to fifty times, preferably 15 to 40 times and most preferably 20 to 30 times. The actual number actually used in the examples herein and presently most preferred are two preparatory breaths followed by a dosing breath and five second breath holding period, with the sequence repeated twenty-four times. The number of breaths in the first and second filter test should be at least that number that will give good distribution of aerosol without significant variation due to breathing variations in the patient. While a large number of breaths reduces variability, this must be balanced with patient abilities, comfort and compliance.

During the second filter test, at each dosing breath a second tracer material is administered to the patient, except this time since filter 161 has been removed and the patient inhales the tracer material. This second tracer material may be the same or different from the first tracer material. As mentioned above, an optional new by-pass

filter 164 that replaces the bypass filter 163 used in the first filter test, or the exhaust filter is now used to measure the amount of blow-by material and the amount of exhaled material from the patient. This breathing sequence and filter collection and measurement allows for correction of the inhaled dose determined in the first filter test to compensate for the amount of material that is inhaled and then exhaled by the patient but never deposited in the patient. The amount of tracer material actually deposited in the patient and its relative ratio to the total amount aerosolized by the inhalation device is then determined.

The results of the first and second filter tests are then used to calculate the number of dosing breaths needed, and optionally the corrections to the inhalation procedure or to the inhalation device, in order to deliver the predetermined dose to the patient in the subsequent administration step. Corrections to the device, if used, typically include resetting the aerosol generation time, the delay time between activation of the nebulizer and aerosolization, pressure used to drive the nebulizer, amount of drug placed in the device, adjustment of the device to obtain a different particle size, and so on. Adjustments in the breathing procedure typically include using a different types of dosing breath, adjusting the breath hold period, using a different type of preparatory breath, changing the number of each type of breath and so on. The patient breathes from the inhalation device used for the tests, or a substantially similar device, for the calculated number of dosage breaths. The number of preparatory breaths between each dosing breath step is typically the same for both filter tests.

Generally it is recommended that at least 15 dosing breaths be required during administration of the drug to minimize breath-to-breath variation. If the determined number of dosing breaths required is less than 10, preferably less than 15, and most preferably less than 20, then the concentration of doxorubicin in the formulation should be reduced. This will have the effect of increasing the number of breaths required to obtain the predetermined dose and reduce the variability due to having one or more breaths in the sequence in which greater or lesser amounts of drug are inhaled compared to the other breaths.

A major advantage of the method of the invention is that the drug with which the patient is to be treated is not used during the first and second filter tests. This reduces risk to the patient. Thus the drug is not present in the patient's system during administration of tracer material, which if radioactive may result in unintended

reactions in the body due to drug/radioactive tracer interaction. In addition, anytime that the three step testing procedure is not used, when only the hereto described two step filter testing method is used without the deposition distribution information, tracer materials having less risk to the patient than radioactive tracers, such as colored or fluorescent markers can be used to determine the number of breaths for proper dosing. In one embodiment for example, the initial filter tests and pulmonary distribution test may be performed using radioactive tracer material with scintigraphy while subsequent tests for the same patient use the filter technique and non-radioactive tracer materials that rely on fluorescence, density, absorption or colored tracer materials.

Use of non-radioactive tracers allows the patient to be tested on the day of treatment immediately before administration of the drug and provides for reducing patient variability from day to day as is further discussed below. A further consideration for using a non-radioactive tracer on the day of treatment with a drug is that some drugs such as some antineoplastic drugs react differently in the body in the presence of radioactive materials. Thus once a test is completed with a radioactive tracer there is typically a washout period of several days to allow radioactive material to clear the body before treatment with the drug. Waiting for the drug washout period to end introduces variability since typically several days elapse between test and administration of the drug. Of course there may be situations where concomitant treatment with drug and radioactive tracer in the body is desired, while this is not the typical case, this method of treatment is contemplated in another embodiment of the invention.

B. Three Step Testing Procedure

The three step testing procedure that is used for patients having substantially impaired pulmonary systems, are at high risk or have other indicia that would , has the same first and second filter tests as the two-step testing procedure discussed above. A third step provides for taking a scintigraphic image of the patient immediately after the second step. This third step provides information as to the distribution of the aerosolized tracer material in the patient. For radioactive tracers, a radiographic image of the patient is made using common imaging techniques. In making the determinations as to amount of inhaled tracer material present at a site, regions of interest are defined in the image. For example, the region of interest may be the

proximal respiratory system, the bronchial tree, a portion of the lungs, or the whole of both lungs. If Tc-99m has been used as the tracer material then the counts in the lungs are determined using imaging techniques. Next the counts in the kidneys, bladder, and those generally attributable to Tc-99m that has left the lungs are determined and these counts are added to the lung counts. Counts in the mouth, stomach and other areas are not counted toward the lung counts. Since the amount of tracer material that has been aerosolized, lost in the system and captured in the by-pass filters 163, 164 and or exhaust filter 140 can be determined, the amount and percentage of tracer material in the lung can be calculated. Decay of radioactive tracer material is corrected by tracking time during the test procedure.

From the information obtained in either the two-step test or the three-step test one can determine the amount of drug to be aerosolized, inhalation device settings needed to obtain the required amount of aerosolized drug to be administered to the patient and the required number of dosing breaths needed to administer the predetermined dose of drug to the patient. In the final step of the method, the drug is administered to the patient for the determined number of dosing breaths with the same inhalation device or a substantially similar inhalation device.

Additional embodiments of the invention include alternate methods of administering the proper dose that is generated and administered to the patient. In the examples herein data generated in the filter tests and in the scintigraphy deposition tests have been used to determine the number of dosing breaths needed to administer the predetermined dose to the patient either as a total body dose or as a pulmonary system or lung dose. While this is the presently preferred method when using the Battelle inhalation device for determining how to properly dose the patient and is believed to provide the most accurate drug dose, alternate methods using time, generated aerosol determinations, and volume or weight changes of supply reservoirs are also contemplated as included within the scope of the invention. These alternate methods may find greater utility when using other inhalation devices. For example, when electrohydrodynamic devices are used to generate the aerosol, volume may be a preferred dosing parameter to provide proper drug dosage.

Thus one additional embodiment for determining the proper dose includes a method of testing and administration utilizing a time period during which the patient inhales aerosol from the inhalation device. This embodiment is achieved by utilizing a time period to administer the tracer material during the first and second filter tests

and then using a time period that may be based in whole or in part on the filter test data to actually administer the drug to the patient. The time periods used in the first and second filter tests would typically be different, with the first filter test time typically shorter than the second filter test time.

Another embodiment for determining the proper dose to be administered to a patient includes a method of testing and administration utilizing the volume of drug that is aerosolized or delivered by the inhalation device. This embodiment is achieved by tracking the amount of tracer material generated as an aerosol or the amount of tracer material that is consumed (reduction in weight or volume) in the nebulizer reservoir during the first and second filter tests. Subsequently, the amount of drug that needs to be generated as an aerosol, or the amount of drug that is to be consumed in the nebulizer reservoir is determined. The determination may be based in whole or in part on the filter test data to actually administer the drug to the patient. The amount of aerosol generated or the reduction in volume or weight of the reservoir material would typically be different. During the first filter test, the amount of aerosol generated or the weight or volume reduction in the reservoir would typically be less than during the second filter test.

C. Patient Classification

A third major embodiment contemplates the classification of patients into two categories and their subsequent treatment. First a determination is made whether the pulmonary function of the patient is substantially normal or substantially impaired; then a determination is made of whether the patient is in a low risk or high risk category for treatment by inhalation with the drug selected for treatment; when the pulmonary function of the patient is determined to be substantially normal and the patient is determined to be in a low risk category for treatment by inhalation with the drug then the patient follows the method using the two step test and administration of drug; when the pulmonary function of the patient is substantially impaired or the patient is in the high risk category for administration of the drug then the patient follows the method using the three step test and administration of the drug.

* * * * * * * * * * *

The following examples are meant to be illustrative of the invention and are not meant to limit the full breadth of the invention disclosed herein.

Comparative Example 1

A subject was tested in a facility, which has equipment, and personnel required to detect gamma radiation by various means. A gamma camera was used to image a radiation source directly to determine the unobstructed (non-attenuated) radiation from the source. A second image was obtained from the posterior side of the subject's chest with the radiation source positioned against the front of the subject's chest. This procedure was repeated with the camera anterior to the chest and the radiation source behind the subject's chest. The difference in the radiation detected by the gamma camera without the subject positioned between the radiation source and the camera and the amount of radiation detected when the subject's chest is placed between radiation source and the camera represents the amount of radiation attenuated by the subject's chest. This difference is converted to percentage radioactivity lost when divided by the amount of radiation detected directly (without the subject present) and is referred to as the attenuation factor.

The subject inhaled an aerosolized solution or suspension containing technetium Tc-99m penetrate (Tc-99m DTPA). After a period of time sufficient to have a measurable quantity of Tc-99m deposited in the respiratory tract, the gamma camera used above to determine the attenuation factor was used to determine the amount of Tc-99m (for example, counts per minute or cpm) in the lungs and upper body of the patient. The previously determined attenuation factor was used to correct the Tc-99m cpm for the attenuation losses. The amount of Tc-99m deposited in the different regions of the respiratory tract was then expressed as a percentage of the amount of Tc-99m aerosolized. Unfortunately the method of this example gave widely varying results that were not easily reproducible even with the same patient. This was due to errors during the correction for attenuation losses. For example the errors related to anatomical differences, imprecise positioning of the patient relative to the gamma camera and so on. The results were therefore off by 40-50% or more.

This example showed the need for a better and easily usable method that would give reproducible results.

Example 2.

The method of the invention using two filter tests eliminates the need to determine the attenuation factor in the aforementioned Example 1 and provides

greater reproducibility. This example illustrates the control of total body dose according to a predetermined dose. The filter tests used alone allow accurate control of total body dose and a reliable dose that is delivered to the pulmonary system as is further explained below.

In the present example, the inhalation device 100 is fitted with an inhalation filter 161 which is capable of removing the Tc-99m that would be inhaled by a patient as well as a blow-by filter 163 to collect Tc-99m which is exhaled. Inhalation filter 161 used to determine the amount of Tc-99m that would be inhaled is placed just before the mouth. The patient is then instructed to inhale the Tc-99m as in Example 1 for a short period of time, (e.g. 0.5 to 2.0 minutes) using a dosing breath pattern of two preparatory breaths followed by a dosing breath and optional breath hold. The preparatory breath and dosing breath sequence is repeated five times. The number of dosing breaths during which Tc-99m aerosol was available is recorded. Filters 161, 163 are then removed from the device and are placed in a well or gamma counters to determine the amount of radioactivity present. For the next step, the second filter test, the patient is instructed to resume the Tc-99m inhalation for a predetermined number of preparatory and dosing breaths (in this case two preparatory breaths for each dosing breath with and optional breath hold and a total of twenty-four dosing breaths, without the inhalation filter 161 in place, for a brief period of time, usually about five minutes. An additional filter 164 can be used to replace filter 163 and can be used to measure blow-by and exhaled aerosol during the second filter test. In the alternative, blow-by aerosol and exhaled aerosol can be determined using only the exhalation filter 140 in the second filter test .

Filter 164 or exhaust filter 140 are measured for radioactivity as well as that for the tubing and the amount remaining in the nebulizer. From this information one can determine the relative amount of aerosol that the patient inhaled compared to the amount actually nebulized. This factor can then be used to determine the required amount of drug that must be nebulized in order to properly dose the patient with a predetermined amount of the drug. If the patient is considered to have substantially normal pulmonary system function so that deposition will follow a pattern determined in previous studies of the deposition patterns of typical patients or of a previous study of this particular patient, then the test stops here. The drug is then administered in accordance to the number of dosing breaths determined from the information developed.

Example 3

This example illustrates the use of the invention to provide accurate predetermined drug dosages to selected parts of the pulmonary system, in this case the lungs. If the patient is determined to have substantial pulmonary system impairment or is determined to not be eligible for the administration of drug according to the method of Example 2 alone, then the patient is quickly placed before a gamma camera. Scintigraphic images of the torso to determine the whole body count and chest and upper abdomen are developed and are used to determine the percentage of Tc-99m present in the lung, kidneys and urinary bladder. The Tc-99m in the kidneys and bladder are added to that in the lung since it is known that inhaled Tc-99m DTPA is excreted via the kidneys. Tc-99m that is swallowed is not absorbed but excreted in the feces and is therefore not counted toward the lung counts.

This method was used for illustrative purposes in a patient (#301) with chronic obstructive pulmonary disease with the following results:

Source of Tc-99m DTPA	cpm/dosing breath	
Nebulized	14,204	
Inhale filter	7,646	
Exhale filter	2,159	
Deposited in body*	5,487	38.6% **

Percentage of total deposited Tc-99m present in lung, kidneys, bladder = 69.7%

Amount of Tc-99m deposited in lung (69.7% x 5,487) = 3,824 cpm/dosing breath

Percentage lung deposition (3,824/14,204) = 26.9%
(The total in the whole body is counted as 100%)

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* Amount inhaled minus the amount exhaled

** Amount deposited in body/amount nebulized X 100

From the data of this example, if one wished to administer a predetermined dose of 10 mg doxorubicin to the lungs of this patient in whom the percentage lung deposition was 26.9%, one would nebulize 37.2 mg of doxorubicin (10 mg ÷ 0.269).

If one used an aerosol generator that delivered 0.32 mg doxorubicin/ dosing breath, this patient would be required to take 116 dosing breaths to receive the predetermined dose of 10 mg (37.2 mg ÷ 0.32 mg/dosing breath).

To illustrate the importance of this method, consider that in four additional patients with impaired pulmonary function, (nos. 403, 404, 405 and 406), the percentage lung deposition was 42.7%, 37.7%, 12.7% and 23.0%, respectively. In order to deposit 10 mg doxorubicin into the lung of these patients, they would require nebulization of 23.4, 26.5, 78.7 and 43.5 mg doxorubicin by taking 73, 83, 246 and 136 dosing breaths. Thus, without the procedure described herein, there is a potential for more than a three-fold error in dosing these four patients.

Example 4.

A method according to Example 2 wherein a patient who has lung cancer and has difficulty in breathing due to constriction of the airways, is given a bronchodilator drug before inhaling the Tc-99m DTPA so as to facilitate the amount of material deposited in the lung and airways.

Example 5.

A method according to Example 3 wherein the information on the distribution of the Tc-99m in the respiratory tract is used to select a particular particle size distribution such that the anticancer drug will be deposited at the tumor site. For example, for those cancers which may be more prevalent in the proximal airways, a larger particle size is preferred. Using the procedure described in Example 3, one could prepare batches of Tc-99m DTPA of specific particle sizes and determine which size provides optimum delivery at the target site. An aerosol of the anticancer drug would be prepared with the same particle size and would be delivered to the target site in the amount calculated per Example 3.

Example 6

This example illustrates a clinical study using the Battelle inhalation device. The study included both healthy volunteers and patients with mild to moderately severe respiratory impairment. The objectives were to evaluate the performance of the inhalation device, the tolerability of the ethanol vehicle and to characterize deposition and distribution of the vehicle with Tc-99m DTPA by means of a filter test and scintigraphy. It was shown that the particle size generated by the Battelle

inhalation device using Tc-99m DTPA in an ethanol/water (20/80,V/V) vehicle was similar to that of doxorubicin in the same vehicle. Because of the similarity of the particle size and other characteristics, a Tc-99m DTPA filter test and the optional scintigraphy test according to the method of the invention can serve as a means of predicting inhalational doxorubicin deposition and distribution and be used to calculate the dosing parameters (e.g. number of dosing breaths a patient will need to take) in order to achieve the deposition of a specific quantity of doxorubicin in the total body, pulmonary system, or lung.

Initially the Battelle inhalation device was programmed for automatic filling of the plenum every third breath. However, it became evident that some subjects, especially patients with impaired respiratory function, were not able to maintain the rhythmic breathing pattern required by the automatic mode operation of the device. Therefore, the option of utilizing a manual operation mode was introduced. In this mode, an operator such as a respiratory therapist operates the aerosol generator, resulting in filling of the plenum when the subject is ready to take a dosing breath. The breathing pattern is typically the same for automatic or manual mode, however, the manual mode provides more flexibility and allows the respiratory therapist to time the filling of the plenum for when the subject is ready to take a dosing breath. With adequate coaching, this manual mode appears to be more appropriate for both the therapist and subjects.

Example 7.

The tests in this example were designed to evaluate the reproducibility of pulmonary deposition of Tc-99m DTPA (10 millicuries in 2 ml 20% ethanol/80% water V/V vehicle) administered by inhalation with the Battelle inhalation device on two occasions at least 7 but no more than 30 days apart to the same person. The differences between this example and Example 6 were that the manual mode was used for operating the delivery device throughout the tests and that patients used a mouthpiece with a mouthseal and noseclip, without a face mask. In Example 6, the patients had noted moderate discomfort with the use of the mask. In the present example, for each of the inhalation tests, the patients followed a set breathing pattern of two normal preparatory breaths followed by a dosing breath and a breath hold - an approximately five second breath hold for each of the twenty-four dosing breaths (approximately 5-7 minutes). Images were obtained immediately after each inhalation

phase to determine pulmonary deposition. Immediately prior to each phase, a filter test was performed to determine the fraction of inhaled dose deposited in the body. Patients were monitored for adverse events, vital signs were assessed and pulse oximetry was obtained during both inhalation phases.

Ten patients with mild to moderately severe respiratory impairment were enrolled into the tests. Patient characteristics are available for 8 patients. Of these, six patients were males, the mean age was 54.9 years (range 27-80 years), and 5 were current smokers. The Karnofsky performance status was 100% for all patients. All except one patient had abnormal chest X-rays. The most frequently noted abnormality was chronic obstructive pulmonary disease. Emphysema or areas of atelectasis were also noted in several patients. Of the pulmonary function tests performed at baseline, the majority were well below the normal reference ranges. In particular, the FEV_1, PEF and D_LCO were well below the normal reference ranges (mean percent reference 56.00%, 56.17% and 49.17 %, respectively). Nine patients underwent both scheduled inhalation phases. One patient withdrew for non-study related reasons after completing the first inhalation phase.

Blood pressure, heart rate and respiratory rate were monitored at intervals throughout and following both inhalation phases. No noteworthy changes were observed except for the expected decrease in respiratory rate and slight increase in diastolic blood pressure. No significant changes in mean oxygen saturation rate were observed. One adverse experience was reported in each of the inhalation phases in one patient. This occurred in a 75 year old female with a history of emphysema, hypoxemia and cardiomyopathy who required oxygen at night. During the first phase the patient developed a coughing spell following the filter collection test requiring a pause in the procedure. Her oxygen saturation declined from 88% (baseline) to 80% but recovered to 86% and the patient completed the inhalation uneventfully. This patient also experienced a coughing spell following the filter collection test preceding the second inhalation, but was able to complete the tests.

Table 3 displays the total body and pulmonary deposition data for the two inhalation phases for the nine patients who completed both phases. Although there were intra-subject differences between the first and second inhalations in both total body and pulmonary deposition, the mean total body deposition (expressed as percent nebulized retained in the body) was 32.44% and 32.78% for inhalation phases 1 and 2 , respectively. The absolute mean difference between the two phases was 3.81

percentage points (range 1.57 to 9.31) with a standard deviation of 2.94. The mean pulmonary deposition (expressed as percent of nebulized retained in the lungs) was 21.70% and 21.46%, for inhalation phases 1 and 2, respectively. The absolute mean difference was 3.19 percentage points (range 0.75% to 5.85%) with a standard deviation of 2.01.

However, for individual patients, the results show an entirely different story. The first three columns in Table 3 list the results for different subjects tested on two different days with the two step filter tests, and shows the percentage of nebulized aerosol that is retained in the body of the subject. The second three columns list results for the same subjects tested on two different days with the two step filter test plus the scintigraphic distribution test that shows the percent of nebulized aerosol that was retained in the lungs. The data for subject Table 3 show that although the retained body aerosol was fairly constant day to day for some subjects (e.g. such as 001, 002, 003) other subjects such as 004 and 008 had large differences. Thus patient 004 would have received about a 30% higher body dose on one day as compared to the next as determined by the filter test and about 25% more in the lung as determined by the filter and scintigraphic tests. Patient 008 would have received about a 35% higher body dose and about a 27% higher lung dose one day compared to the next.

A further review of Table 3 shows even though the means discussed above are small for all subjects and standard deviations are not large, differences between individuals can be quite large. On day 1, subject 006 had a retained body dose of aerosol of 43.9 % while subject 008 had a retained body dose of 26.8 %. If these individuals had been given standard doses subject 006 would have received a 64 % higher body dose than subject 008. On day 2, subject 006 would have received a 44 % higher dose than subject 004. Similarly on day 1, subject 006 would have received a 100 % larger dose of aerosol that was retained in the lung than subject 001. On day two, subject 006 would have received a 44 % larger dose of aerosol that was retained in the lung than subject 001, and a 62 % larger dose than subject 002. Although the data in Table 3 have not been corrected for differences in nebulizer output, the data clearly illustrate the large differences in individual variations in dose that can be obtained by inhalation. For drugs that are highly toxic (e.g. antineoplastic drugs) or those having narrow therapeutic windows this variation is simply not acceptable. Further, as shown in Table 1 the large differences in dosage illustrated above, when neoplastic drugs are involved, can lead to immediate death.

Table 4 lists results for tests that were intended to show the variability between different nebulizers of the same type. Again the nebulizer used with this example was the one used in the Battelle inhalation device. These data show the nebulizer output in mL for each dosing breath taken by the subject. The data was generated using a different nebulizer on each test day for each subject. Thus no subject was ever treated twice with the same nebulizer. The mean volume of tracer material per dosing breath, averaged over the 29 dosing breaths, was .023 mL with a range of .0199-.0272 mL. The highest nebulizer output was found with patient 001 on day 1 while the lowest nebulizer output was found with subject 006 on day 1. This represents a low to high percentage output difference of about 37 %. When one considers that when the drug is administered to the patient this difference could be added to the difference found between patients or on different days with the same patient, one can clearly see the need for the present invention in delivering consistent doses to a patient.

Pulmonary distribution, as determined scintigraphically, revealed greater deposition in the right than in the left lung. The difference in deposition between the two lungs was statistically significant. However, the mean difference was small (1.03%, range -0.19 to 2.72%).

The present invention can correct for the differences between patients and for the same patient on different days or in different parts of a patient's treatment particularly when the patient is tested and treated according to the precepts of the present invention. The present invention is especially efficacious when testing and treatment are closely spaced in time as within a few days or most preferably on the same day. The present invention can eliminate the differences in inhalation devices by testing the patient with the device immediately prior to treatment with a drug by using a non-radioactive easily tolerated tracer in the filter tests.

Table 3

Same patient and Inter-patient Deposition Variability for Inhaled Tracer Material Aerosols on Two Different Test Days

	Percent of Nebulized Retained In Body (%)			Percent Nebulized in Total Lung (%)		
Subject ID	**Day 1**	**Day 2**	**Absolute Difference**	**Day 1**	**Day 2**	**Absolute Difference**
001	32.36	35.86	3.50	15.56	17.60	2.04
002	30.55	28.91	1.64	18.42	15.69	2.73
003	29.05	30.62	1.57	21.74	22.49	0.75
004	36.40	28.08	8.32	26.04	20.19	5.85
005	26.87	29.10	2.24	21.65	23.11	1.46
006	43.90	40.33	3.57	31.15	25.41	5.74
008	26.76	36.07	9.31	18.85	23.87	5.02
009	31.06	28.99	2.07	21.32	20.19	1.13
010	35.03	37.06	2.03	20.56	24.57	4.01
N	9	9	9	9	9	9
Mean	32.44	32.78	3.81	21.70	21.46	3.19
Standard Deviation	5.41	4.55	2.94	4.56	3.28	2.01

Table 4

Volume of Tracer Material per Dosing Breath[1]
For Individual Subjects

Patient	Vol/Breath
001.1	0.0272 mL
001.2	0.0227 mL
002.1	0.0229 mL
002.2	0.0228 mL
003.1	0.0202 mL
003.2	0.0232 mL
004.1	0.0216 mL
004.2	0.0256 mL
005.1	0.0234 mL
005.2	0.0216 mL
006.1	0.0199 mL
006.2	0.0237 mL
008.1	0.0256 mL
008.2	0.0242 mL
009.1	0.0242 mL
009.2	0.0252 mL
010.1	0.0222 mL
010.2	0.0244 mL
mean	0.0232 mL
Standard Deviation	0.00199

1 - Volume loaded was 2.0 mL and a total of 29 dosing breaths for all subjects

2 - The first three digits in the subject designation represents the patient number (e.g. 001), the digit after the period represents the test day (1st or 2nd), (e.g. 001.1 designates data for patient 1 taken on the first test day; 001.2 designates data for patient 1 taken on the second test day.

Example 8

This example further illustrates the determinations and calculations in the filter tests and Tc-99m deposition Test discussed in detail elsewhere herein. The dosing parameters for administering the predetermined dose of drug to the patient will be determined based on the filter tests (as total body dose) or the Tc-99m deposition pattern test by scintigraphy (as pulmonary deposited dose) and in the main embodiment will be expressed as the number of dosing breaths that the patient will have to inhale. The calculations are described in detail below.

The patient should be comfortably seated and fitted with a suitable mouthpiece. A nose clip is preferably used to prevent breathing through the nose. Appropriate site personnel, usually a respiratory therapist, will undertake patient coaching and operation of the inhalation device. Once the patient is ready to begin, there will be a brief training session until the patient is familiar with the required breathing pattern. The patient will be instructed to breathe normally for several preparatory breaths (preferably two) followed by instructions to take the proper dosing breath (e.g. "breathe deeply and hold for so many seconds" if deep lung deposition is desired) during which the patient is to take the proper dosing breath and breath hold. For deep lung deposition the instruction would be to take a deep breath to full lung capacity with a breath hold of preferably 1 to 30 seconds and most preferably about 1 to 10 seconds. After the patient is comfortable with this breathing pattern the filter tests and the tracer material inhalation will begin followed by the pulmonary deposition tests it desired.

The Battelle inhalation device will be readied and 10 millicuries of Tc-99m DTPA will be added to 2ml of the vehicle in a syringe and injected into the inhalation device. The amount of radioactivity in the aerosol generator, in this case when a nebulizer is used, the " nebulizer charge" is recorded.

The Tc-99m filter test is designed to determine the fraction of the inhaled aerosol that is deposited in the patient and to quantify the "blow-by" aerosol which is not available to the patient for inspiration. It consists of two filter tests.

1) Filter test -For the first filter test, two filters, an inhalation filter (immediately in front of the mouthpiece) and a "blow-by" filter will be inserted into the inhalation device (see Figures 1 and 2 for details). The patient will be instructed to breathe normally for two breaths followed by a "breathe deeply and hold for a count of five"

instruction by the therapist. Prior to the "breathe deeply and hold" instruction, towards the end of the second normal inspiration, the therapist will activate the solenoid by pressing and releasing the pendent switch. The filter test continues with the breathing pattern of two normal preparatory breaths followed by a dosing breath for a total of five dosing breaths. The number of dosing breaths taken (corresponding to the number of plenum fills) will be shown on the display panel of the Battelle inhalation device. At the end of the first filter test, the Battelle inhalation device will be turned off and the mouthpiece and nose clip temporarily removed. The two filters (inhalation filter and blow-by filter) will be removed for measurement of radioactivity by counting in a gamma well counter. A gamma camera anterior image of the patient's lungs will be obtained. The same Battelle inhalation device, restored to its original configuration without the two additional filters 161, 163 , will be used, and the second filter test will begin.

In the second filter test the patient will be refitted with the mouthpiece 125 and noseclip 121. Throughout the second filter test, the breathing pattern will continue with two normal preparatory breaths followed by a dosing breath and five-second breath hold with the therapist activating the inhalation device as described above. The duration of the second filter test is typically twenty-four dosing breaths (approximately 5-7 minutes). It is expected that this will result in the deposition of approximately 2mCi Tc-99m DTPA in the lungs. Upon completion of the 24 dosing breaths, the Battelle inhalation device 100 will be turned off and the mouthpiece 125 and nose clip 121 will be removed. An additional filter, the replacement by-pass filter 164 or, the exhaust filter 140, which was in place throughout the procedure, will be removed for gamma counting using a dose calibrator. Additional anterior images of the lungs and also of the abdomen will be obtained and the distribution of radioactivity present in the lungs, kidneys and bladder will be determined.

A gamma well counter (dose calibrator) is typically used to assay small items (inhalation and blow-by filters) and a gamma camera is typically used for the larger items (gas lines, exhaust filter, etc.), however the gamma camera can be used for all items if desired.

Listed below is the procedure to calculate the total deposited dose. The calculations are based upon data from a two part Tc-99m tracer material filter test for the total body dose and upon data from the optional three part test for the pulmonary dose. Subject #403 completed the tests as outlined herein. The first filter test had two

preparatory breaths for each dosing breath with a five second breath hold, this sequence was repeated five times. During the second filter test two preparatory breaths were taken for each dosing breath with a 5 second breath hold, this procedure however, was repeated only for a total of 16 dosing breaths rather than the desired 24. The calculations below take this into account in determining dosing parameters for the total body dose and the pulmonary dose.

Correction of Dose Calibrator Counts to Gamma Camera Counts

Approximately 0.5 mCi Tc-99m is introduced into a 250 mL saline bag that only has approximately 50 mL of saline. This saline bag is measured for radioactivity in a dose calibrator as well as using the gamma camera. The ratio of radioactivity determined by the gamma camera to that obtained by the dose calibrator is used to correct all dose calibrator counts to gamma camera radioactivity.

Abbreviations:

BF	Blow-by filter
IF	Inhalation Filter
Ex	Exhaust
DE	Deposition Efficiency
DB	Dosing Breath
cpm	Counts per minute

Inhalation filter (MF) – the amount of tracer material, Tc-99m, on the inhalation filter represents the amount of material that would be inhaled with the required number of dosing breaths, in this case, five dosing breaths.

Blow-by filter (BF) – the amount of tracer material, Tc-99m, on the blow-by filter represents the amount of material that was aerosolized, but by-passed the mouthpiece and was not available to the subject for inhalation during the required number of dosing breaths.

Exhaust (Ex) – the amount of tracer material, Tc-99m, on the exhaust filter and in the exhaust tubing represents the total amount of exhaled tracer material and the amount of blow-by tracer material.

Deposition Efficiency (DE) – the fraction of the nebulized material, tracer material or drug, that is deposited (retained) in the body.

The following data are required for calculating the total deposited dose:

- Pre-Syringe Gamma Counts
- Saline Bag Gamma Counts
- Number of Dosing Breaths during the First Filter Test
- Inhalation Filter Counts following the First Filter Test
- Blow-by Filter Counts following the First Filter Test
- Number of Dosing Breaths during the Second Filter Test
- Exhaust Filter or Second Blow-by Filter Counts following the Second Filter Test
- Amount Remaining in Nebulizer following the second filter test
- Post-Syringe Gamma Counts

Detailed Calculations:

1) All counts must be adjusted for Tc-99m decay by conversion from time acquired to a standard timepoint such as 12:00, assuming a half-life of 6 hours for Tc-99m.

$$A_1 = A_0 e^{\frac{-0.693t}{T_{1/2}}}$$

where t = time elapsed

$T_{1/2}$ = radionuclide half-life

e = base of natural logarithm

A_o = activity in the original sample

A_1 = activity after a period of elapsed time

2) Express radioactivity in cpm.

3) Determine amount inhaled per dosing breath.

Am't inhaled (cpm/DB) = Inhalation Filter (cpm) / no. of dosing breaths in filter test

4) Determine amount of blow-by.

Am't Blow-by (cpm/DB) = Blow-by Filter (cpm) / no. of DB in the first filter test

5) Determine the total number of dosing breaths (DB) taken during the first filter test and the second filter inhalation test phase. If the Tc-99m deposition pattern test is performed in accordance with the protocol, the number of dosing breaths for the first filter test should be five and the number of dosing breaths for the second filter test should be "24". The total number of dosing breaths for the Tc-99m two filter tests would be "29". Since only 16 dosing breaths were taken during the second filter test the total number of dosing breaths was 21.

6) Determine amount exhaled.

Am't exhaled (cpm/DB) = (Exhaust (cpm)/No. of dosing breaths in the second filter test)

- Blow-by (cpm/DB)

7). Determine amount nebulized.

Amt. nebulized (cpm) = Pre-Syringe cts (cpm) – Post-syringe cts (cpm) – amt remaining in nebulizer (cpm)

8) Determine amount nebulized per dosing breath (DB).

Am't nebulized per DB (cpm/DB) = Am't nebulized (cpm) ÷ total No. of DB during Tc-99m deposition test

9) Determine amount deposited (retained) in the body.

Am't deposited (cpm/DB) = Am't inhaled (cpm/DB) from No. 6 above – Am't exhaled (cpm/DB) from No. 8 above

This number is the total deposited dose.

10) Determine Deposition Efficiency.

Deposition Efficiency = Am't deposited (cpm/DB) from No. 9 above / Am't nebulized (cpm/DB) from No. 5 above

The calculations below illustrate the determinations and procedures that are outlined above. A patient to be treated is first tested with the device as described with data obtained as shown in Table 5 and Table 6 below.

Table 5

PARTS	**COUNTS in cpm***	IMAGE TIME (min)	DOSE CALIB (mCi)	CLOCK TIME
Pre-syringe	1,070,522	2	9.98 8.8914 (to 12:00)	11:00
Saline Bag	51,050	2	0.424	12:00
Inhalation Filter	33,017	2	0.255	12:00
Blow-by Filter	15,882	2	0.119	12:00
Post-syringe	28,978	2	0.22	12:00
Nebulizer	819,922	2	6.81	12:00
Exhaust	66,693	2		

*These counts are already corrected for decay.

Table 6

TEST	**Number of Dosing Breaths**	**Time of Breaths** (min)
First Filter test	5	1.5
Second Filter test Inhalation	16	5

STEP 1 – Decay to the same timepoint.

$$A_1 = A_0 e^{\frac{-0.693t}{T_{1/2}}}$$

where t = time elapsed
$T_{1/2}$ = radionuclide half-life
e = base of natural logarithm
A_0 = activity in the original sample
A_1 = activity after a period of elapsed time

For example, assume there were 31,602 counts with the clock time of 12:08:48. If one corrects to 12:00, t = 8.8 min. Therefore,

$$A_1 = 31{,}602\, e^{\frac{(-0.693)(-8.8)\text{min}}{360\ \text{min}}} = 31{,}602 \text{ X } 1.0171 = 32{,}142 \text{ counts}$$

STEP 2 – Express radioactivity in cpm.

To convert the pre-syringe counts from the dose calibrator, one first must decay the 9.98 to 12:00 using the equation in step 1.

$$A_1 = 9.98 \text{ mCi } e^{\frac{-0.693\,(1\text{ hr})}{6}} = 8.8914 \text{ mCi}$$

Tc-99m in the saline bag is used to convert radioactivity measured in the dose calibrator to cpm obtained by gamma camera imaging. Thus, the pre-syringe corrected time (8.8914 mCi) is converted to cpm as follows:

$$\frac{\text{Decayed saline bag (cpm) x decayed pre-syringe dose calibration (mCi)}}{\text{Decayed saline bag dose calibration (mCi)}}$$

$$= \frac{51{,}050 \text{ cpm x } 8.8914 \text{ mCi}}{0.424 \text{ mCi}} = 1{,}070{,}533 \text{ cpm}$$

STEP 3: Determine amount inhaled.

Amt inhaled (cpm/DB) = Inhalation filter (cpm) / no. of dosing breaths in filter test
= 33,017 cpm / 5 dosing breaths
= 6,603 cpm/DB

STEP 4: Determine amount of blow-by.

Am't Blow-by (cpm/DB) = Blow-by filter (cpm) / No. of dosing breaths in filter test

= 15,882 / 5 dosing breaths

= 3,176 cpm/DB

STEP 5: Determine Total Number of Dosing Breaths.

The total number of dosing breaths is the sum of the number of dosing breaths during the filter test and the number of dosing breaths during the second filter test. In the above example, the total number of dosing breaths is equal to 21 (5 + 16).

STEP 6: Determine amount exhaled.

$$\text{Am't Exhaled (cpm/DB)} = \frac{\text{Exhaust (cpm/DB)}}{\text{No. of dosing breaths second filter test}} - \text{Blow-by (cpm/DB)}$$

$$= \frac{66{,}693\text{cpm/DB}}{16\text{ DB}} - 3{,}176\text{ (cpm/DB)}$$

$$= 4{,}168 - 3{,}176\text{ (cpm/DB)}$$

$$= 992\text{ cpm/DB}$$

STEP 7: Determine the amount nebulized.

Amt nebulized (cpm/DB) = pre-syringe cts (cpm) – post-syringe cts (cpm) - amt remaining in nebulizer (cpm)

= 1,070,522 cpm – 28,978 cpm – 819,922 cpm

= 221,622 cpm

STEP 8: Determine amount nebulized per dosing breath.

$$\text{Am't nebulized (cpm/DB)} = \frac{\text{Am't nebulized(cpm)}}{\text{Total No. of dosing breaths during Tc-99m deposition test}}$$

= 221,622 cpm / 21 dosing breaths

= 10,553 cpm/DB

STEP 9: Determine amount deposited (retained) in the body.

Amt deposited (cpm/DB) = Amount inhaled (cpm/DB) – Amount exhaled (cpm/DB)

= 6,603.4 – 992

= 5,611 cpm/DB

STEP 10: Determine Deposition Efficiency.

Deposition Efficiency = Am't deposited (cpm/DB) / Am't nebulized (cpm/DB)

= 5,611 / 10, 553

= 0.532 or 53.2%

The deposition efficiency from step 10 can then be used to determine various dosing parameters for administering the antineoplastic drug on a total body basis.

Calculations for Pulmonary Deposited Dose

Once the total body dose is determined as above, the dose deposited in the pulmonary system or a region of interest within the pulmonary system can be determined. For example the counts in the pulmonary system, bladder, and kidneys can be added since it is know that Tc-99m exits the lung as is explained in one of the examples. The ratio of the pulmonary dose to the total body dose then gives the percent deposited dose for the pulmonary system. A similar calculation can be done for a region of interest within the pulmonary system.

Table 7 illustrates the radioactive counts per minute (cpm) for various regions of the body and the clock times associated with the measurements.

Table 7

Area	Counts	Decayed CPM	Duration of Image, Min	Clock Time
Left Lung	31,602	16,071	2	12:08:48
Right Lung	30,923	15,726	2	12:08:48
Chest Total	70,316	35,759	2	12:08:48
Left Kidney	Data not available			
Right Kidney	Data not available			
Bladder	1,476	757	2	12:13:06
Abdomen Total	20.656	10,592	2	12:13:06

STEP 11: Determine total counts for the body.

$$\text{Total Body (cpm)} = \text{Total Chest (cpm)} + \text{Total Abdomen (cpm)} = 35{,}759 + 10{,}592 = 46{,}351 \text{ cpm}$$

STEP 12: Determine total lung.

$$\text{Total Lung(cpm)} = \frac{\text{Left Lung + Right Lung + Bladder + Left Kidney + Right Kidney}}{\text{Total Body Counts}}$$

(Note: Data for kidneys may not always be available, as in this example.)

$$\text{Total Lung (cpm)} = \frac{16{,}071 + 15{,}726 + 757}{46{,}351} = \frac{32{,}554 \text{ cpm}}{46{,}351 \text{ cpm}}$$

$$= .7023 \text{ or } 70.23\%$$

STEP 13: Determine amount in lung.

$$\text{Amount in lung (cpm/DB) in cpm/DB} = \text{Total Lung Counts x Amount Deposited in Body} = .7023 \times 5611 = 3940.6 \text{ cpm/DB}$$

STEP 14: Determine fraction deposited in lung

$$\text{Fraction Deposited in Lung} = \frac{\text{Amount in Lung (cpm/DB)}}{\text{Amount nebulized (cpm/DB)}}$$

$$= \frac{3{,}941}{10{,}553}$$

= .3734 or 37.34 %

The fraction deposited in the lung (deposition efficiency) can be used to determine the proper dosing parameters on a region of interest. In this case the lungs. Example 3 shows how the deposition fraction or efficiency is used to calculate a dosing parameter, in that case the number of dosing breaths required to administer a predetermined dose to a patient.

EXAMPLE 9

This example illustrates an actual treatment of a patient using the procedures described herein and particularly the detailed description of Example 8. The patient treated suffered from an untreatable cancer in the spinal region that had metastasized to the lung and was in need of inhaled chemotherapy to treat the lung metastases. The patient had already been treated by IV for cancer of the spinal cord with doxorubicin. The patient was evaluated as described earlier and found to be in the low risk category and thus eligible for the low risk method described herein. There was no detectable blockage and the patient exhibited only small scattered metastases distributed throughout the lung. The patient exhibited full lung capacity. Other signs of being at high risk were absent. Although the patient could have been treated with the procedure of the low risk category, because the drug is very toxic and the tests in their early stages it was determined to proceed with the patient as if the patient were in the high-risk category.

The patient's body surface area was determined using the nomograms for calculating adult body surface area published in ASFS Drug Information 96, Gerald K McEvoy, Ed., American Society of Health-System Pharmacists, page 2780. The patient weighed about 64 kg and had a height of 160 cm. Thus the calculated body surface area used was about 1.7 m^2. The baseline pre-syringe counts per minute of injected test material were 1,352,918 cpm. The number of deep breaths during the filter test was five (5) for which the plenum was filled five (5) times with fresh nebulized material. The counts on the mouth filter that would correspond to the inhaled portion were 26,494 cpm or 5,299 cpm per deep breath. The counts for the blow-by filter test were 24,364 cpm or 4,873 cpm per deep breath. The plenum was filled 24 times with fresh nebulized material during the test. The counts on the exhaust (including exhaust filter and exhaust tubing) were 130,438 cpm or 5,435 cpm

per deep breath. The number of deep breaths for the mouth and blow-by filters was five (5) and the number of deep breaths for the exhaust was 24 for a total of 29 deep breaths for the entire deposition test. The amount remaining in the nebulizer was 1,019,308 cpm. Thus the amount nebulized was calculated to be 10,595 cpm per deep breath. The exhaled dose (exhaust - blow-by) was 562 cpm per deep breath and the deposited dose (mouth filter dose - exhaled dose) was 4,737. This resulted in an overall deposition efficiency (deposited dose ÷ amount nebulized) of about 0.45. It was determined that this patient was to receive single doses of doxorubicin of 0.4 mg/m^2 body surface area by inhalation.

The volume of drug inhaled per deep breath was calculated for 29 breaths using the procedure outlined in the earlier examples to be 15.8 microL per deep breath.

It was known that animals (in this case dogs) could tolerate 4 mg/m^2 of doxorubicin when given by mouth tube. For the patient 1/10 of this dose or 0.4 mg/m^2 was chosen as the initial dose. This dose could be escalated or decreased depending on the response of the patient. If the patient reacts negatively to the dose (e.g. extreme coughing etc.) the dose can be reduced in increments such as in 25% - 50% steps until a tolerable dose is obtained. Likewise if there is no response to the administered doses (i.e. no control of tumor growth) the doses can be increased in increments of 10% to 100% until an efficacious dose or a dose limited by toxicity is found.

Table 8 illustrates the counts per minute (cpm) for various parts of the body during the scintigraphic test. The measurements are correlated to clock times for correction of decay as needed. The amounts in the kidneys in this case were negligible, however, in other embodiments particularly with other tracer materials these measurements may be important. The amounts of tracer material entering the blood stream from ingested tracer material in the stomach were previously found not to contribute to amounts in the kidneys and bladder.

Table 8

Area	Counts cpm	Duration of Image, Min	Start Clock Time/ Military time	Stop Clock Time/ Military time
Left Lung*	32,730	2.0	15:19	15:21
Right Lung*	42,617	2.0	15:19	15:21
Mouth	2,392	2.0	15:19	15:21
Trachea	2,140	2.0	15:19	15:21
Chest Total	98,128	2.0	15:19	15:21
Stomach	6772	2.0	15.23	15:25
Left Kidney*	0	2.0	15.23	15:25
Right Kidney*	0	2.0	15.23	15:25
Bladder*	0	2.0	15.23	15:25
Abdomen Total	19,194	2.0	15.23	15:25

* All of these are calculated as lung deposition since the source of radiation in the kidneys and bladder are from inhaled portions.

The patient was given the Tc 99m deposition test as described earlier with the results shown in Table 8. The nebulizer was filled with 2 mL of a 20% ethanol in water solution containing 10 mC Tc 99m DTPA. The patient then inhaled five (5) deep breaths with the mouth filter and blow-by filter in place. A gamma camera was then used to image the patient's lungs to verify that no Tc 99m had been inhaled. The latter measurement served as the background level. The mouth filter and blow-by filter were then removed for determination of radioactivity deposited on the filters and the patient was then instructed to take 24 additional deep breaths without the filter in place. The patient was then placed under a gamma camera for scintigraphic analysis and subsequent quantification of the distribution of the Tc 99m-DTPA in the lung and other organs. The exhaust filter and associated conduits were evaluated for deposition.

The radioactivity data (cpm) was collected and the number of deep breaths of doxorubicin aerosol required were calculated from the radiation counts in the filters and from the organs as noted above . A desired deposited dose of doxorubicin of 0.4 mg/m^2 with a body surface area of 1.7 m^2. With a total body deposition efficiency of

0.45 a total dose of 0.68 mg of doxorubicin was required. The supplied doxorubicin formulation had a concentration of 4 mg/mL. Since each pulse delivered 0.092 mg, the number of required deep breaths was determined to be sixteen (16) (see calculation below:

0.68 (total DOX dose) ÷ 0.45 (deposit efficiency) ÷ 0.092(DOX per pulse) = 16.4 or about 16 deep breaths.

The patient came in for treatment once every three weeks for a total of three doxorubicin treatments by inhalation. The daily course of treatment of 0.4 mg/m^2 gave an overall dose of 1.2 mg/m^2 for the total course of treatment. The lung tumors did not grow during this time and the patient exhibited no ill effects. The doses were well tolerated and the procedure was successful in avoiding toxicity and providing a controlled dose.

While the forms of the invention herein disclosed constitute presently preferred embodiments, many others are possible. It is not intended herein to mention all of the possible equivalent forms or ramifications of the invention. It is to be understood that the terms used herein are merely descriptive, rather than limiting, and that various changes may be made without departing from the spirit of the scope of the invention

METHOD FOR SAFELY AND EFFECTIVELY ADMINISTERING A DRUG BY INHALATION

CLAIMS

We claim:

1. A method for administering a drug to a patient by inhalation in a safe and effective manner comprising:

A. determining whether the pulmonary function of said patient is substantially normal or significantly impaired;

B. determining whether said patient is in a low risk or high risk category for treatment by inhalation with said drug; and

C. (1) when the pulmonary function of said patient is determined to be substantially normal and said patient is determined to be in a low risk category for treatment by inhalation with said drug, administering said drug to said patient by the steps comprising:

a. performing a first filter test on said patient with an inhalation device and a tracer material to obtain patient inhalation data;

b. performing a second filter test on said patient with said inhalation device and said tracer material to obtain patient deposition data;

c. determining dosing parameters from data obtained in Steps C(1)a and C(1)b for using said inhalation device to deliver a safe and effective dose of drug to said patient; and

d. administering said drug to said patient with said inhalation device or a substantially similar inhalation device according to said dosing parameters determined in step C(1)c; or

(2) when the pulmonary function of said patient is determined to be significantly impaired or said patient is determined to be in a high risk category for treatment by inhalation with said drug, administering said drug to said patient by the steps comprising:

a. performing a first filter test on said patient with an inhalation device and a tracer material to obtain patient inhalation data;

b. performing a second filter test on said patient with said inhalation device and said tracer material to obtain patient deposition data;

c. performing a scintigraphic analysis on said patient immediately after Step C(2)b to obtain patient distribution data;

d. determining dosing parameters from data obtained in Steps C(2)a, C(2)b and C(2)c for using said inhalation device to deliver a safe and effective dose of drug to said patient; and

e. administering said drug to said patient with said inhalation device or a substantially similar inhalation device according to said dosing parameters determined in step C(2)d.

2. The method according to Claim 1, wherein said dosing parameter determined is the number of dosing breaths required from said patient.

3. The method according to Claim 1, wherein said dosing parameter determined is the time during which said patient breathes said drug.

4. The method according to Claim 1, wherein said dosing parameter determined is the amount of aerosol produced while said patient breathes said aerosol.

5. The method according to Claim 1, wherein the dosing parameter determined is the difference in weight or volume in a source of drug while said patient breathes an aerosol produced from said drug source.

6. The method according to Claim 1, wherein said drug is an antineoplastic drug.

7. A method for administering a drug to a patient by inhalation in a safe and effective manner comprising:

a. performing a first filter test on said patient with an inhalation device and a tracer material to obtain patient inhalation data;

b. performing a second filter test on said patient with said inhalation device and said tracer material to obtain patient deposition data;

c. determining from data obtained in Steps a and b the dosing parameters for using said inhalation device to deliver a safe and effective dose of drug to said patient; and

d. administering said drug to said patient with said inhalation device or a substantially similar inhalation device according to said dosing parameters determined in Step c.

8. The method according to Claim 7, wherein said dosing parameter determined is the number of dosing breaths required from said patient.

9. The method according to Claim 7, wherein said dosing parameter determined is the time during which said patient breathes said drug.

10. The method according to Claim 7, wherein the dosing parameter determined is the amount of aerosol produced while the patient breathes said aerosol.

11. The method according to Claim 7, wherein the dosing parameter determined is the difference in weight or volume in a source of drug while said patient is breathes an aerosol produces from said drug source.

12. The method according to Claim 7, wherein said drug is an antineoplastic drug.

13. A method for administering a drug to a patient by inhalation in a safe and effective manner comprising:

a. performing a first filter test on said patient with an inhalation device and a tracer material to obtain patient inhalation data;

b. performing a second filter test on said patient with said inhalation device and said tracer material to obtain patient deposition data;

c. performing a scintigraphic analysis on said patient, after Step b, to obtain tracer material distribution data;

d. determining from data obtained in Steps a, b and c the dosing parameters for using said inhalation device to deliver a safe and effective dose of drug to said patient; and

e. administering said drug to said patient with said inhalation device or a substantially similar inhalation device according to the dosing parameters determined in Step d.

14. The method according to Claim 13, wherein said dosing parameter determined is the number of dosing breaths required from said patient.

15. The method according to Claim 13, wherein said dosing parameter determined is the time during which said patient breathes said drug.

16. The method according to Claim 13, wherein said dosing parameter determined is the amount of aerosol produced while said patient breathes said aerosol.

17. The method according to Claim 13, wherein said dosing parameter determined is the difference in weight or volume in a source of drug while said patient is breathes an aerosol produces from said drug source.

18. The method according to Claim 13, wherein said drug is an antineoplastic drug.

19. An inhalation device for administering a tracer material and a drug to a patient comprising:

A. an aerosol generator;

B. a patient interface for administering a tracer material and said drug to said patient, connected to said aerosol generator so as to receive an aerosol therefrom; and

C. a tracer material within said aerosol generator, wherein said tracer material when aerosolized has substantially the same deposition pattern in said patient as said drug.

20. An inhalation device for administering a tracer material and a drug to said patient comprising:

A. an aerosol generator;

B. a patient interface, having a mouthpiece for dosing a patient, an inlet and an outlet, wherein said inlet is connected to said aerosol generator for receiving aerosol from said generator;

C. a removable filter at said mouthpiece for filtering aerosol;

D. a removable filter at said outlet for filtering exhaled and blow-by aerosol;

E. a tracer material within said aerosol generator, wherein said tracer material when aerosolized has substantially the same deposition pattern in said patient as said drug.

21. Any and all novel features or combination of features, disclosed in the specification of this application.

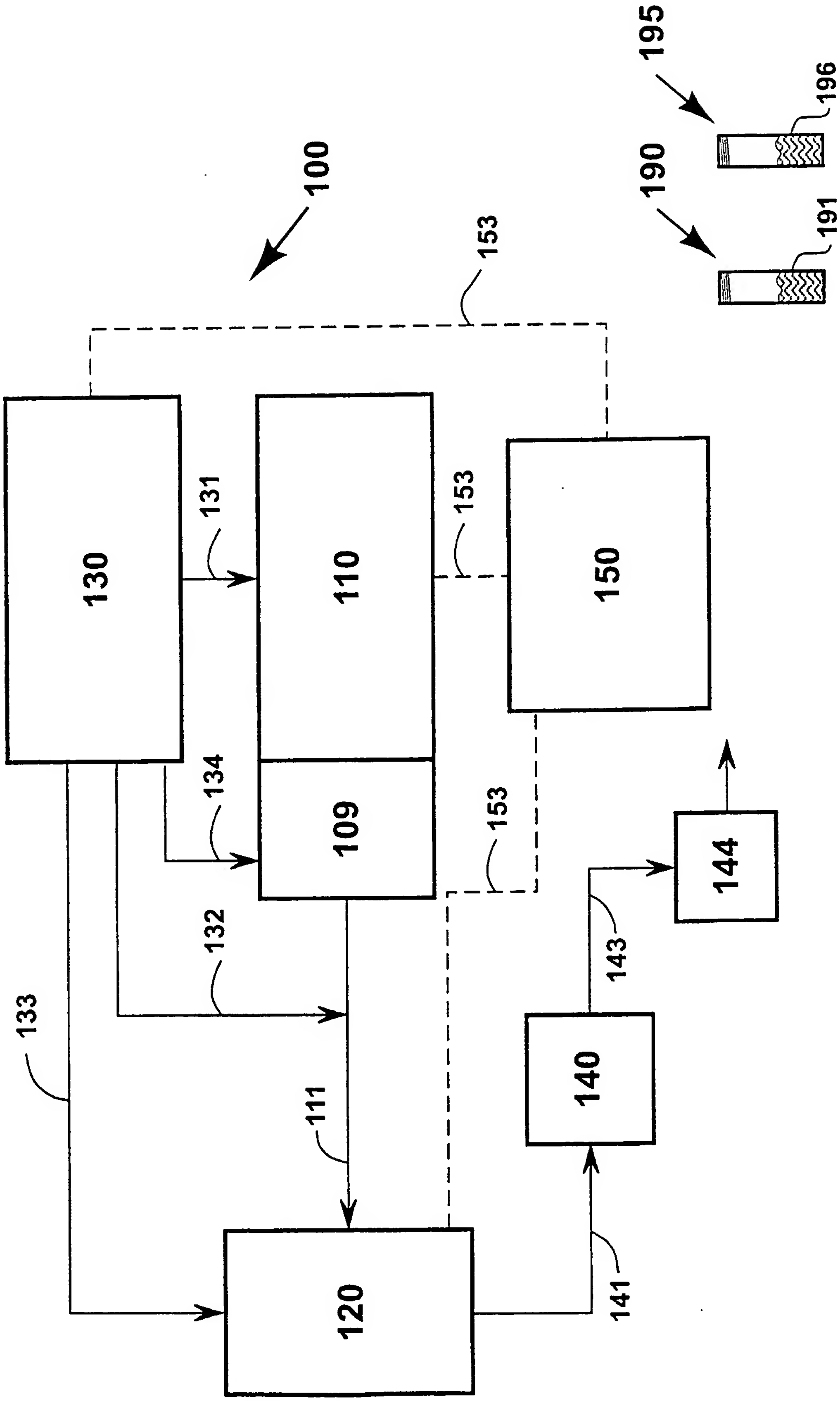
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FIG. 1

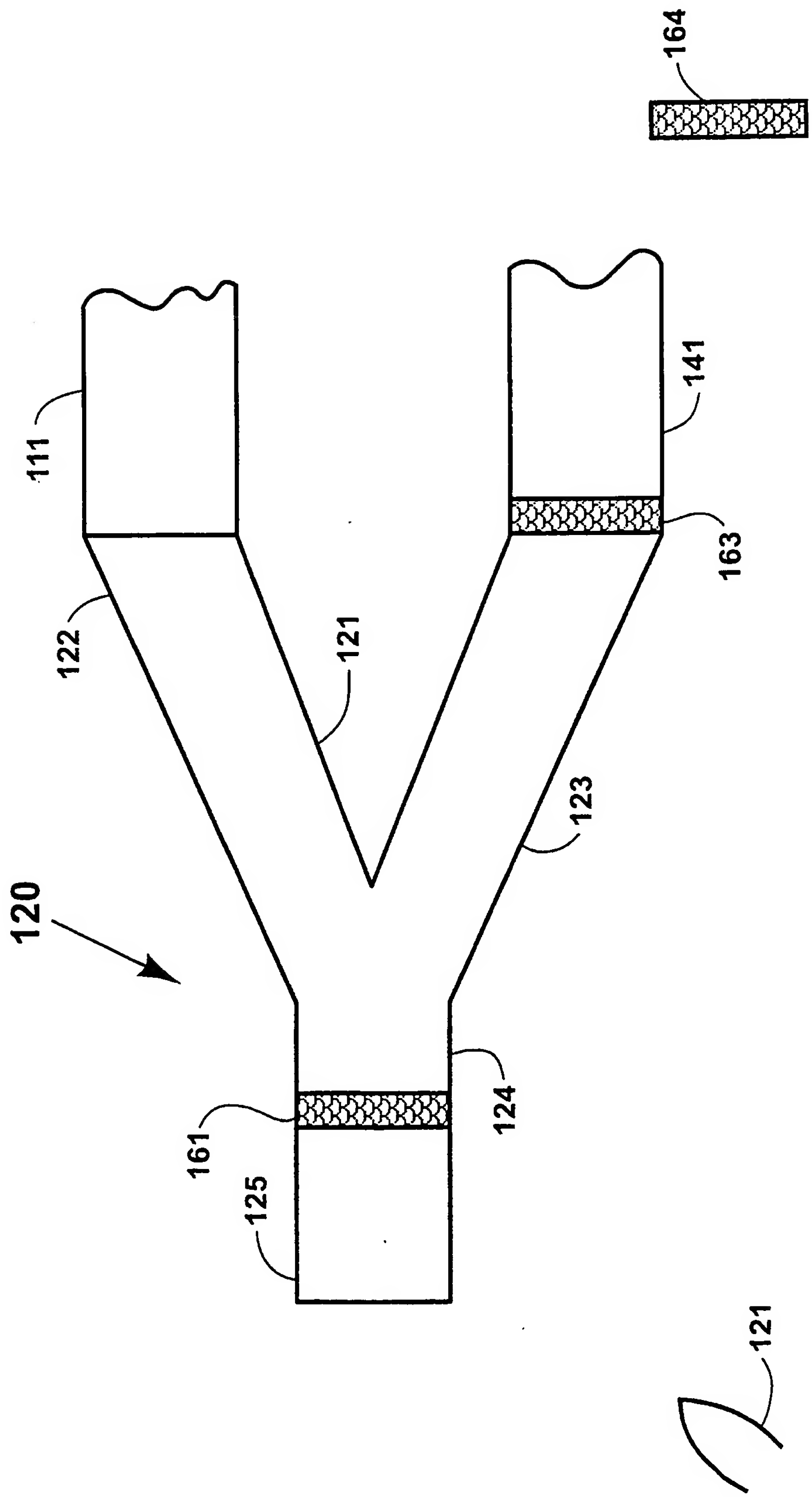

FIG. 2

INTERNATIONAL SEARCH REPORT

Inter   nal Application No
PCT/US 00/05559

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/08 A61M15/00 A61M15/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 44664 A (BATTELLE MEMORIAL INSTITUTE) 10 September 1999 (1999-09-10) cited in the application the whole document	19,20
X	US 4 741 331 A (WUNDERLICH ALAN) 3 May 1988 (1988-05-03) abstract; figure 7	19,20
X	US 4 703 753 A (BORDONI MAURICE E ET AL) 3 November 1987 (1987-11-03) abstract; figure 4	19,20
A	US 5 829 436 A (FARR STEPHEN J ET AL) 3 November 1998 (1998-11-03) abstract; figure 3	19,20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 May 2000	07/06/2000

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INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 00/05559

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 302 834 A (SOLCO BASEL AG) 8 February 1989 (1989-02-08) abstract; figure 1	19,20
A	DE 23 46 730 A (HEYER GMBH CARL) 17 April 1975 (1975-04-17) the whole document	19,20

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[rnatio]nal Application No
PCT/US 00/05559

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9944664 A	10-09-1999	AU 2896899 A	20-09-1999
US 4741331 A	03-05-1988	NONE	
US 4703753 A	03-11-1987	US 4823784 A,B	25-04-1989
		US 4510929 A	16-04-1985
US 5829436 A	03-11-1998	CA 2245079 A	07-08-1997
		EP 0955885 A	17-11-1999
		WO 9727804 A	07-08-1997
		AU 2117897 A	22-08-1997
		US 5792057 A	11-08-1998
EP 0302834 A	08-02-1989	CA 1315897 A	06-04-1993
		JP 1131643 A	24-05-1989
		US 5139016 A	18-08-1992
DE 2346730 A	17-04-1975	NONE	